THE FISSION

OF

AROMATIC KETONES

Thesis submitted for the degree of

Doctor of Philosophy.

Alexander Thomson B.Sc.

May 1955

University of Edinburgh.

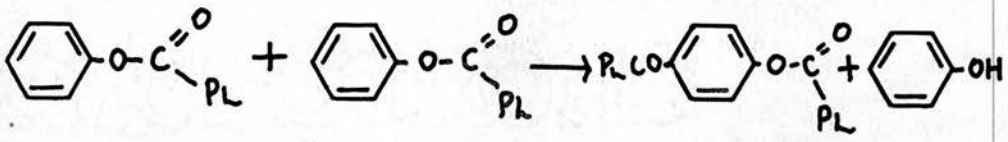
THE UNIVERSITY *of* EDINBURGH

INDEX

INTRODUCTION

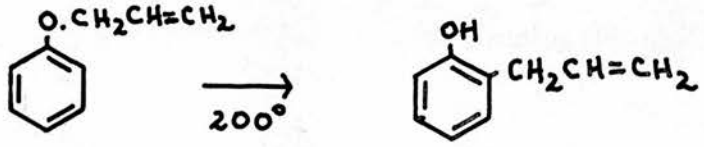
In 1908 Fries discovered that an acyl derivative of a phenol, when heated with aluminium chloride with or without a solvent, is changed into the isomeric ortho- or para-hydroxy ketone or a mixture of both.

The mechanism suggested is an intermolecular one in which there is a migration of the acyl group from one molecule to the ortho or para position in the second molecule viz.,



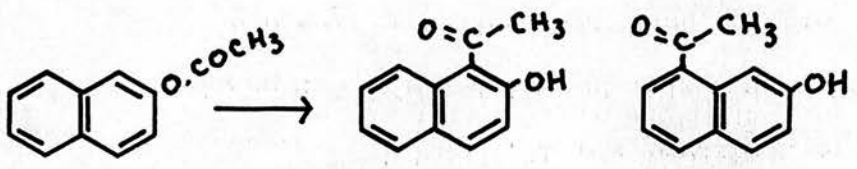
However, a great deal of evidence has been brought forward in favour of an intramolecular mechanism and no definite conclusions have yet been drawn[1].

A similar reaction to this is the Claisen Rearrangement in which the allyl groups in phenolic allyl ethers migrate from the phenolic oxygen to the aromatic nucleus, on heating viz.,



The Fries reaction has been used extensively in the syntheses of ortho- and para- hydroxy aromatic ketones. The ketonic groupings which migrate may be aliphatic (as in o- hydroxyacetophenone) or aromatic (as in p- hydroxybenzophenone). Many examples of the synthetic use of the reaction have been investigated. Wilson Baker and co-workers[2] [3] have carried out a great deal of work in this field. They have, for example, extended the use of the reaction to the syntheses of hydroxy ketones in the hydrindene series where the molecule involved is only partly aromatic.

Much more recently many Indian workers have been active in this field. Joshi and Shah[4] report the formation of a 2, 8- substituted naphthalene by Fries migration. They found that treatment of β- naphthyl acetate (I) gave a small yield of a ketone which they have proved to be 2- hydroxy- 8- acetylnaphthalene (III). The main product however was the 1, 2- isomer (II).



I II III

This method therefore affords a simpler way of obtaining the phenol (III) than the more tedious method employed by Leonard and Hyson[5].

Auwers[6] and Baddeley[7] have shown that the Fries migration of an alkyl substituted aromatic nucleus may be accompanied by an additional isomerisation of one or more alkyl groups to a new position in the molecule. This second

isomerisation is brought about by the use of an additional molecule of catalyst in the reaction (i.e. two molecules of aluminium chloride in all).

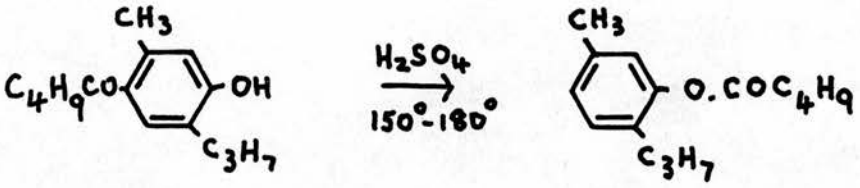
Several other reagents have been used to catalyse the Fries migration. Aluminium bromide has been used successfully when aluminium chloride has been shown to be too drastic[8] (p. 80). Bruce and co-workers[9] have recently reported the use of a sodium chloride- aluminium chloride melt in the formation of hydroxy ketones. This method has the recommendation of a very short reaction time (two minutes at 180°) and the yields are similar to those obtained by the more conventional methods of synthesis of the ketones.

Other reagents which have been used are ferric chloride[10] and titanium tetrachloride. The latter seems to be a very effective catalyst and it would appear to be a useful reagent when aluminium chloride catalysed rearrangements fail or give small yields. It has the added advantage of being fairly cheap and readily obtainable.

The Fries Reaction therefore, has a fairly wide application in the synthesis of aromatic hydroxy ketones which are often quite difficult to obtain by the normal methods such as Friedel-Crafts and Grignard reactions. The rearrangement is becoming more and more important in the preparation of dyestuff intermediates and antiseptics. Use of this reaction has been made in the preparation of many of the ketones investigated in this Thesis and it has proved a very simple and effective method in most cases.

This Thesis describes the investigation of a reaction, which was thought might be a reversal of the Fries migration - a reaction first observed by Rosenmund and Schnurr[11]. They noticed that, under certain conditions, several p-hydroxy ketones could be converted into phenol esters. The requisites, both structural and experimental, for the reverse reaction have been carefully studied. The p- hydroxy ketone must contain a substituent ortho to the acyl group and the rearrangement is effected by heating with sulphuric, camphorsulphonic, or phosphoric acid.

Rosenmund and Schnurr showed, for example, that treatment of a hydroxy ketone such as 2- methyl- 4- hydroxy- 5- isopropyl butyl ketone (IV) with several drops of concentrated sulphuric, and subsequent heating to 150-180°, gave an almost quantitative isomerisation into the corresponding ester, thymol isovalerate (V).



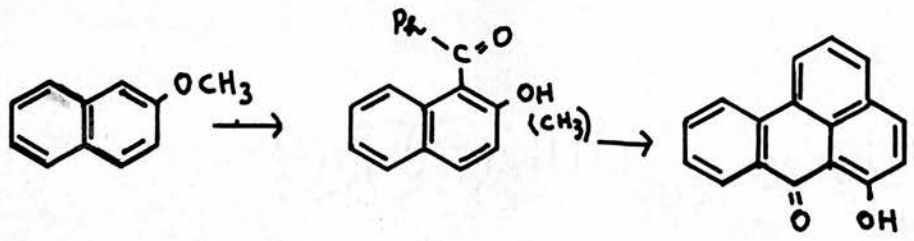
IV V

Several other ketones were found to give similar results. 2- Methyl- 4- hydroxyacetophenone rearranged to give m-cresol acetate. The corresponding phenacetyl and benzoyl ketones rearranged similarly. Ester formation was complete in 30 - 60 minutes in most cases.

This work by Rosenmund and Schnurr clearly shows that the migration is a reversal of the normal Fries isomerisation.

The reagent used in the present work was hydrobromic acid in glacial acetic which was found to bring about a similar ketonic fission of a hydroxyl substituted aromatic ketone.

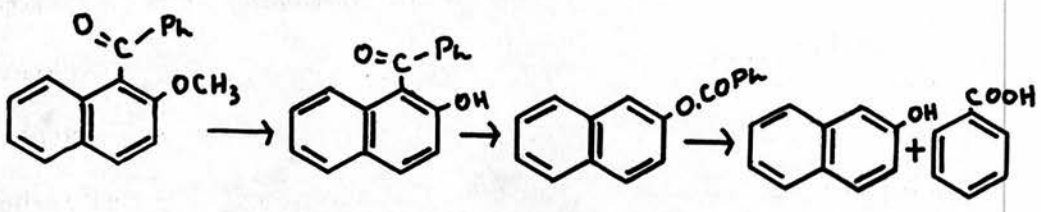
The work began after Woodham[12] had noticed a ketonic cleavage while carrying out synthetic work in the mesobenzanthrone series. He was trying to synthesise 6-hydroxymesobenzanthrone (VIII) by a cyclisation of 1-benzoyl- 2- hydroxynaphthalene (VII) using aluminium chloride and sodium chloride.



VI VII VIII

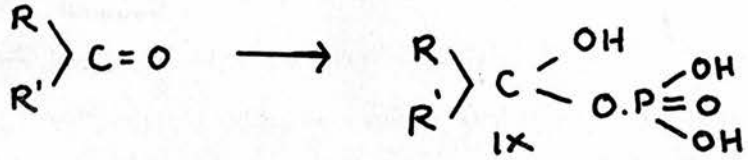
In the preparation of the intermediate (VII) however, he found that the Friedel-Crafts reaction with benzoyl chloride and 2- methoxynaphthalene (VI) gave 1- benzoyl- 2- methoxynaphthalene almost entirely. This was contrary to Fieser's work [13] who obtained an excess of the hydroxy ketone. To obtain this hydroxy ketone Woodham decided to demethylate the methyl ether with hydrobromic acid in glacial acetic, which is a common demethylating reagent. He found that demethylation and debenzoylation both occurred and the product was β- naphthol in good yield with no evidence of the hydroxy ketone. It was considered possible that this is an example of the Reverse Fries Reaction. The ester of the phenol however is not obtainable in the acidic

conditions of the reaction medium; its formation would be followed by an immediate hydrolysis presumably. It was thought that the mechanism might be:- Fission of ketone → Ester → Phenol + Acid, viz.,



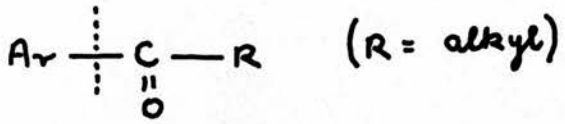
Many reagents, both acidic and alkaline, have been shown to cause ketonic fission and a review of those will be given.

Among the earliest examples is the use of phosphoric acid. In 1885 Louise [14] found that 2:4:6-trimethylbenzophenone (benzoylmesitylene) gave the hydrocarbon mesitylene and benzoic acid on treatment with this reagent. Following this a large number of ketones were prepared by Klages and Lickroth[15] and treated with phosphoric acid. They found in many cases that crystalline "double compounds" consisting of one molecule of ketone and one molecule of acid were formed. These were said to be phosphoric acid "esters" of the type (IX).

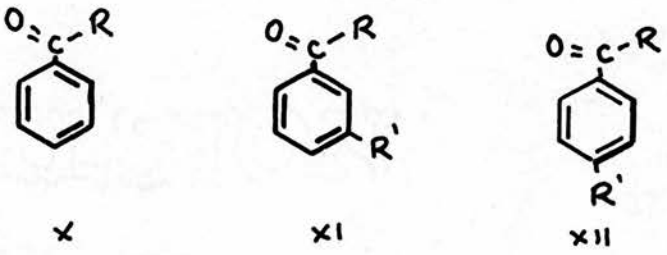


IX

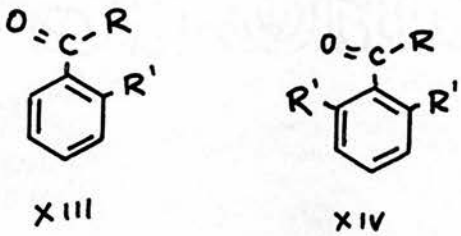
When these so called esters were heated fission of the ketone into the parent hydrocarbon occurred. The fission was shown to have taken place between the aromatic nucleus and the carbonyl side chain as shown by the dotted line:-



These workers found that alkyl substituted ketones of the types (X), (XI) and (XII) showed no signs of fission. i.e. unsubstituted, meta and para substituted ketones such as acetophenone, 3- methyl- and 4- methyl- acetophenone (R = R' = CH_3 in (X), (XI) and (XII)).



X XI XII



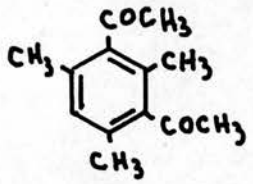
XIII XIV

Fission, however, did take place with ketones of types (XIII) and (XIV) which have ortho and di-ortho substituents respectively. With ketones such as 2- methylacetophenone yields of 20 - 30% hydrocarbon were obtained after an eight hour treatment in excess of syrupy phosphoric acid. On the other hand ketones with two ortho groupings in the nucleus gave quantitative yields of hydrocarbon.

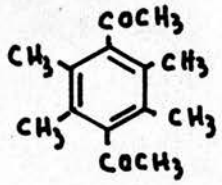
Treatment of 2:4- dimethylacetophenone, 2- methyl- 5- isopropyl- and 2:3:5- trimethyl- propiophenone curiously enough gave the same percentage yields of hydrocarbon

material. 3:4- Dimethylacetophenone, however, gave a smaller yield as expected.

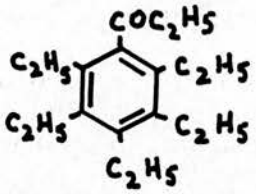
Similarly ketones such as diacetylmesitylene (XV), diacetyldurene (1:4- diacetyl- 2:3:5:6- tetramethylbenzene) (XVI), 2:4:6- trimethylacetophenone and 2:3:4:5:6- pentaethylpropiophenone (XVII) were completely split. All these ketones have two ortho substituents.



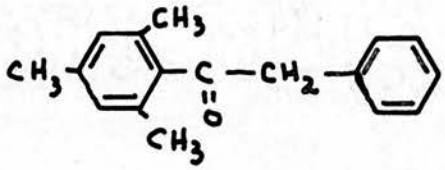
XV



XVI



XVII



XVIII

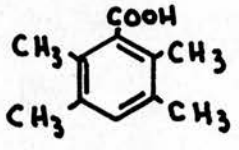
The deoxybenzoin, 2:4:6- trimethyldeoxybenzoin (XVIII) was quantitatively decomposed whereas its unsubstituted counterpart showed no sign of fission.

From this experimental data these workers noted that the nature of the side chain, the number, nature and position of the alkyl groups were of importance in this fission reaction. They also stressed that the stereochemical factor must not be forgotten. For example the size of the alkyl groups and the bulkiness of the side chain in a 2,6- substituted ketone viz., (XVIII) must play a part in the ease (or difficulty) of the commencement of fission. They found, however, that 2:4:6- trimethyl- and 2:4:6-

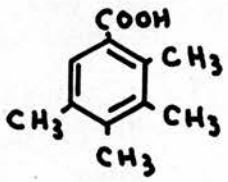
triethyl- acetophenone gave equivalent yields of fission products although the ethyl groups are more bulky than the methyl. It was noted that the benzoyl ketones, corresponding to the acetophenones mentioned above, were apparently more difficult to split. 2:4- Dimethylbenzophenone and the 2:4:6- trimethyl and triethyl ketones gave smaller yields of hydrocarbon material than the corresponding acetophenones. Benzophenone, like acetophenone, was unchanged.

It is worthy of note that p- methoxyacetophenone (after four hours heating) and p- methoxypropiophenone (after ten hours) are reported to have yielded 40% and 70% fission product, respectively. No mention of demethylation of the ethers is reported and so this cleavage cannot be said to be taking place by the Reverse Fries reaction.

The relationship between this type of fission and the decarboxylation of carboxylic acids has been noticed. 2:4:6- Trimethylbenzoic, when refluxed in phosphoric, was decarboxylated to the extent of 50% after 10 minutes and 70% after four hours.

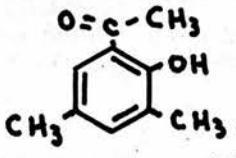


XIX

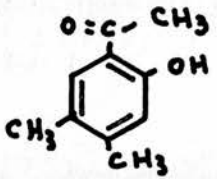


XX

2:3:5:6- Tetramethylbenzoic acid (XIX) reacted similarly but the unsymmetrical isomeric acid (XX) was recovered unchanged.



XXI



XXII

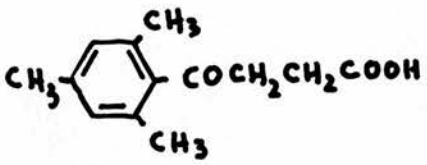
Other workers[16] [17] have employed phosphoric acid in this way to remove ketonic side chains from various alkyl substituted xylenols such as 2- hydroxy- 3:5- dimethylacetophenone and 2- hydroxy- 4:5- dimethylacetophenone (XXI) and (XXII) respectively. They used a tenfold excess of reagent (84% orthophosphoric acid).

Rosenmund and Schnurr[11] report that phosphoric acid is an effective reagent in bringing about the Reverse Fries reaction with substituted phenolic ketones.

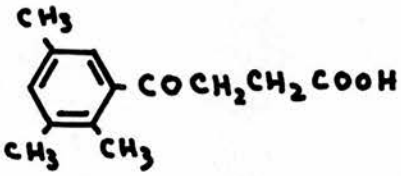
Another reagent which has been used to effect the fission of ketonic side chains from aromatic nuclei is hydrochloric acid. In 1895 Muhr[18] used this acid in an attempt to decompose certain benzoylpropionic acids. He found that benzoylpropionic acid itself $C_6H_5COCH_2CH_2COOH$ was unchanged after five to nine hours at 150° - 200°. Similarly p- methylbenzoylpropionic acid gave no fission products. However 2:4- dimethylbenzoylpropionic acid gave a quantitative yield of m- xylene. Likewise the corresponding acids from ortho- and para- xylene both cleaved. The yields of hydrocarbon were in the order m- xylene > p- xylene > o- xylene (trace only).

As in the work of Klages and Lickroth[15] several alkyl substituted acids were prepared and allowed to undergo reaction with hydrochloric acid. The position of the alkyl groups was again found to be important - the yield of hydrocarbon from 2:4:6- trimethylbenzoyl- propionic acid (XXIII) being greater than that from the

unsymmetrical isomer 2:3:5- trimethylbenzoylpropionic acid (XXIV).



XXIII



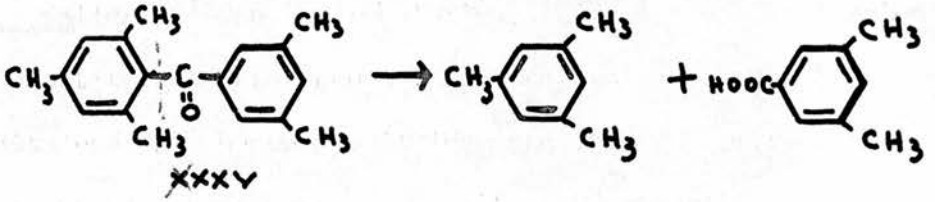
XXIV

Weiler[19] used hydrochloric in his work on the fission of substituted benzophenones. He reports yields of 48% mesitylene from benzoylmesitylene and 15% from 2:4:6;3';5'- pentamethylbenzophenone (XXV) with the production of 3:5- dimethylbenzoic as the other fission product in this latter case. Fission must therefore have taken place as indicated by the dotted line in (XXV). Elbs[20] reports similar findings on treatment of alkyl substituted benzophenones under fairly similar conditions.

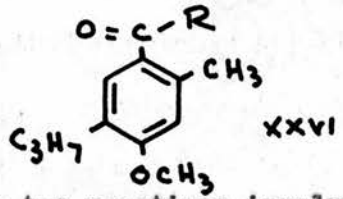
Cook[21] also examined the effect of hydrochloric acid on several anthracene derivatives with interesting results. 9- Benzoyl- 10- hydroxyanthracene loses its benzoyl grouping but 9- benzoylanthracene is unchanged showing the necessity of the presence of the hydroxyl grouping in a favourable position. 9- Benzoyl- 10- nitroanthracene and the corresponding chloro and bromo derivatives give no fission after four hours treatment with a solution of the acid in glacial acetic acid.

Royer[22], in 1953, noticed that the demethylation of 2- methyl- 4- hydroxy- 5- isopropylacetophenone methyl ether with pyridine hydrochloride gave varying yields of the phenol

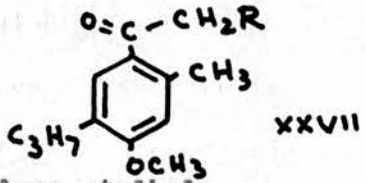
because of a competing fission reaction of the ketonic side chain. This was the instigation of further work by several French chemists and Royer and Bisagni[23], Chalvet, Royer et al.[24], have developed some interesting ideas on the mechanism of the reaction. They prepared several aromatic and aliphatic ketones, from the methyl ether of thymol, of the types (XXVI) and (XXVII).



XXXV



XXVI



XXVII

The two reactions involved have been studied:

(a) The demethylation of the phenol

$$CH_3O - Ar - COR \longrightarrow HO - Ar - COR$$

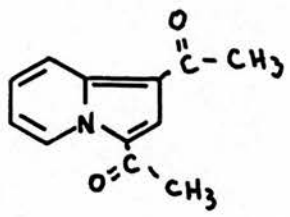
and (b) the ketonic fission

$$CH_3O - Ar \vdots COR \longrightarrow HO - Ar + RCOOH$$

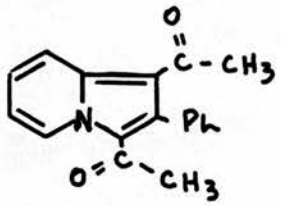
A discussion of the two changes taking place is given and the mechanism of fission, from the point of view of the relationship between possible structural changes in the molecule (e.g. tautomerism) and the ease of fission (from a bond dissociation energy standpoint), is developed in some detail. This is referred to later in the Thesis.

Scholtz[25] and Borrows[26] reported that acyl substituted pyrrocolines are readily deacylated by mineral acids. 1:3- Diacetylpyrrocoline (XXVIII) gives pyrrocoline after treatment with hydrochloric acid[25] and 1:3- diacetyl-

2- phenylpyrrocoline (XXIX) is deacetylated by heating the acidic solution of the compound on the steam bath for two minutes[26].

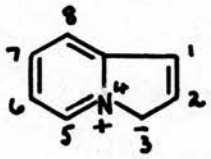


XXVIII

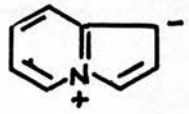


XXIX

A ready explanation of this is forthcoming from the application of the resonance theory to pyrrocoline. The aromatic character of the compound can be attributed to the unshared electrons on the nitrogen atom resonating among all the atoms of the ring.

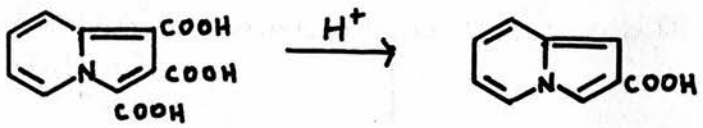


XXXa.



XXXb.

The main contributing forms have been shown to be (XXX a) and (XXX b) by Wilson[27] and Ochiai[28]. That the 1- and 3- positions are indeed reactive has frequently been established and the decarboxylation of carboxyl groups in those positions but not in the 2- position of pyrrocoline- 1:2:3- tricarboxylic acid (XXXI) affords good evidence for an increased electron density at the 1- and 3- positions[29].



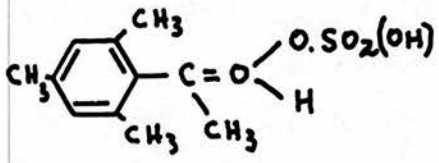
XXXI

Nitration and Friedel-Crafts reactions take place at these positions too so there is no doubt that fission of the ketonic groupings will take place fairly readily.

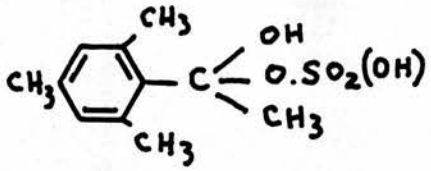
Concentrated sulphuric acid is another mineral acid which has been successfully employed to achieve this ketonic fission reaction. Among the earliest examples of its use is that of the work of Claus[30]. Following some earlier work by Markstahler (unpublished), who found that the action of this acid on benzoylmesitylene gave mesitylene-1- sulphonic acid and benzoic acid, Claus prepared 2-methyl- 5- isopropylbenzophenone which gave benzoic acid and the corresponding sulphonic acid after three hours treatment at 100°.

Hoogewerff and van Dorp[31], in the course of work on the addition products formed between mineral acids and various organic compounds, noticed that ketonic fission sometimes took place. Among the ketones examined were 2:4:6- trimethyl-, 2:3:5:6- and 2:3:4:5- tetramethyl-acetophenone. The relationship between the position of the alkyl groups and the ease of fission was examined, the close link between the ease of decarboxylation of the corresponding acids, when ortho substituents were present, and this cleavage being noted. Further, the similarity between the effect of substituents on this reaction and on acetal formation of substituted aldehydes[32] is mentioned.

The addition compounds with sulphuric acid are envisaged as being of types (XXXII a) or (XXXII b).



XXXII a



XXXII b.

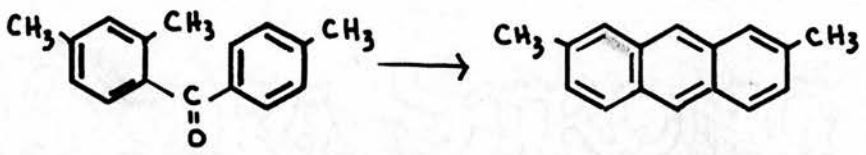
(XXXII b) is to be preferred as it avoids the presence of a quadrivalent oxygen as in (XXXII a). Such compounds, it is noted, are likely to be very unstable and so fission would appear to be a possibility when they decompose.

Elbs[20] has also, indirectly, found examples of a fission reaction with sulphuric acid. While trying to synthesise anthracene derivatives from 2:5-dimethylbenzophenone by cyclisation, he noticed that benzoic acid was produced from the reaction. This could only mean that the benzophenone molecule had been degraded. Another ketone he studied was 1- benzoylnaphthalene, which, on treatment at 150°, gave the naphthalene sulphonic acid and benzoic acid. All the phenyl ketones he studied gave similar results, cleavage and subsequent sulphonation taking place.

Cook[21] used a solution of concentrated sulphuric in acetic acid in an attempt to cleave the benzoyl grouping from 9- benzoylanthracene. Complete decomposition was achieved in thirty minutes. Similar treatment of 9-benzoyl- 10- nitro, 9:10- dibenzoyl and 9- benzoyl-

9:10- dihydro- anthracene gave no fission products even after three hours. The corresponding bromo and chloro ketones were found to give tarry products only.

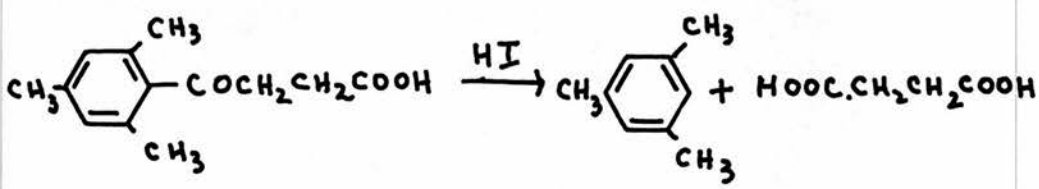
Morgan and Coulson[33], in their work on the syntheses of some substituted anthracenes, prepared as an intermediate 2:4:4'- trimethylbenzophenone (XXXIII) which, on heating, gave 2:7- dimethylanthracene (XXXIV).



XXXIII XXXIV

In an attempt to improve the yield and to speed up this removal of the elements of water, these workers used acetic anhydride, fused zinc chloride and concentrated sulphuric as dehydrating reagents. With concentrated sulphuric they found that ketonic fission took place to give m- xylene and p- methylbenzoic acid.

Hydriodic acid, being a strong mineral acid, must be expected to be equally effective in the cleavage of ketones. Several workers have reported examples of this. Meyer[34] attempted to reduce 2:4:6- trimethylbenzoylpropionic acid (XXXV) to the corresponding butyric acid, in an analogous way to the method employed for the reduction of benzoylformic acid.



XXXV

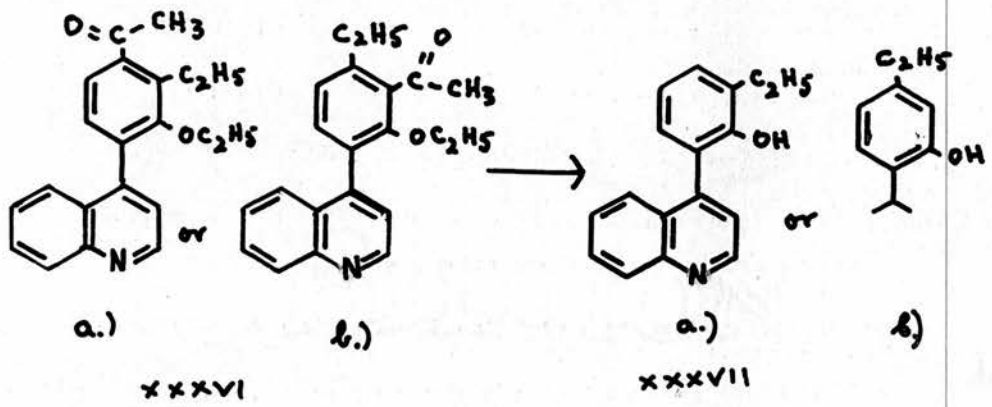
He used hydriodic acid as the reducing agent. Instead of reduction, however, mesitylene and succinic acid were produced. Meyer attributes this fission to the presence of the carboxylic acid group in (XXXV). It is noteworthy that the corresponding trimethylbenzoylformic acid gave no fission into the hydrocarbon and oxalic acid.

Another worker in this field[19] reported the fission of some substituted benzophenones when treated with this acid and red phosphorus. Klages[35] has even used the reagent to remove alkyl groups in substituted benzenes, viz., the removal of the 1- methyl- in 1:2:4:6- tetramethylbenzene and the propyl grouping in 1- propyl- 2:4:6- trimethylbenzene.

The reagent used in the present work has been found to give ketonic fission with a number of ketones. A mixture of hydrobromic acid and glacial acetic acid has been used extensively as a demethylating reagent for the decomposition of ethers, especially in the carbohydrate field. In fact many of the examples of ketonic fission were noted while carrying out such demethylation or de- alkylation reactions.

One of the earliest examples of its use as a demethylating reagent with aromatic ethers is reported by Stoermer[36] who used a mixture of glacial acetic and hydrobromic acid to demethylate o-, m- and p- methoxybenzophenone as well as the 2:4'- dimethoxy ketone. The treatment was carried out under reflux for one hour to an hour and a half. No fission is reported.

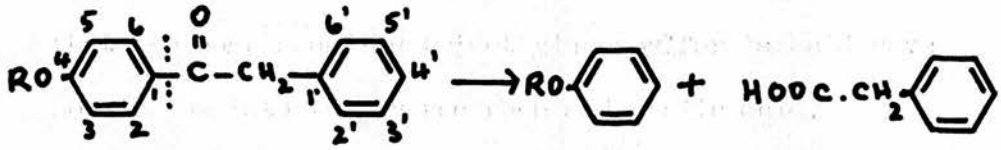
Koenigs[37] showed that 4- [2- ethoxy- 3(or 4)- ethyl- 4(or 3)- acetyl- phenyl]- quinoline (XXXVI) gave 4-[2- hydroxy- 3(or 4)-ethyl- phenyl]- quinoline (XXXVII) on treatment with 48% hydrobromic acid for two hours. So ketonic fission had taken place as well as de-ethylation.



The structure of this compound (XXXVI) has not been settled, as the relative positions of the ethyl and acetyl groups cannot be decided. From general considerations it would seem that (XXXVI b) is correct as the ether grouping $-OC_2H_5$ is in a position ortho to the ketone. In the structure (XXXVI a) the ketone is meta to the phenolic ether and fission would not be so likely. The question is complicated by the quinoline nucleus however, and steric factors may influence the reaction.

A more recent and systematic report on the use of hydrobromic acid in glacial acetic was made by Hill and Short[38]. They used equal parts of each acid and treated the ketones for two hours under reflux. They investigated

several substituted deoxybenzoins of the type (XXXVIII) which were found to undergo fission, to the corresponding phenol and substituted acetic acid, as shown by the dotted line in (XXXVIII).



XXXVIII

From their results they worked out a table of the ketones in order of decreasing ease of fission:-

(A) a) 4- methoxy- 2:4'- dimethyldeoxybenzoin.

b) " " 2:2' " " " (100%)

(B) " " 2- methyl " " (100%)

(C) " " " " acetophenone (79%)
(not a deoxybenzoin)

(D) 4'- nitro- 4- methoxy- 2- methyldeoxybenzoin.

(E) 4- methoxy " "

(F) a) unsubstituted.

b) 2'- methyl " "

The last two ketones F(a) and F(b) were found to be completely stable and (D) and (E) only slightly decomposed. Several conclusions were drawn from this work:-

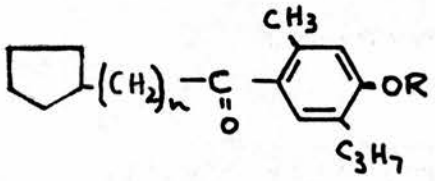
1) Fission occurred only when the phenyl nucleus contained a hydroxyl or methoxyl group.
2) The fission process was facilitated by the presence of an ortho methyl group in the same nucleus.
3) It was retarded however, by a nitro group in the benzyl nucleus.

4) An ortho- or para- methyl group in the benzyl nucleus also accelerated the cleavage.

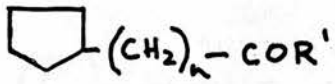
5) Benzyl ketones underwent fission more readily than the corresponding methyl ketones e.g. B > C in the table above.

From these conclusions the mechanism of the reaction is discussed briefly and a relationship to that investigaged by Rosenmund and Schnurr is suggested.

Buu-Hoi and Cagnaint[39] noticed a similar type of ketonic fission during work in the synthesis of ketones of the type (XXXIX) and (XL).

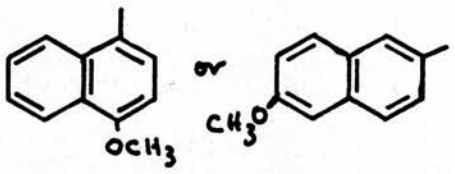


XXXIX



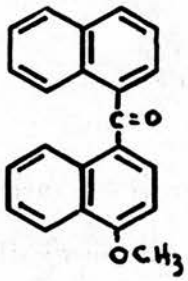
XL

R = H or CH_3 ; $n = 10, 11, 12$

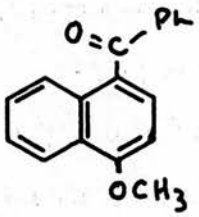
R' = 

They treated the ketones with excess hydrobromic acid in acetic acid for twelve hours. In an earlier paper (40) these workers noted that 1- naphthoyl- 4- methoxynaphthalene (XLI) undergoes decomposition on similar treatment. They are of the opinion however that the ketone 1- benzoyl- 4- methoxynaphthalene (XLII) will undergo demethylation only. The present work has shown that this idea is erroneous (see p. 65).

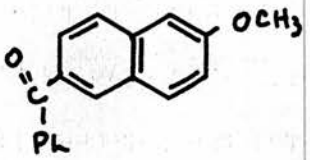
The report of the fission of the ketone (XL) (with R = 6- methoxynaphthyl-) is interesting as it has been shown, indirectly, that the corresponding 2- methoxy- 6- benzoylnaphthalene (XLII) did not undergo fission on similar treatment, the demethylated ketone only being obtained (41).



XLI



XLII

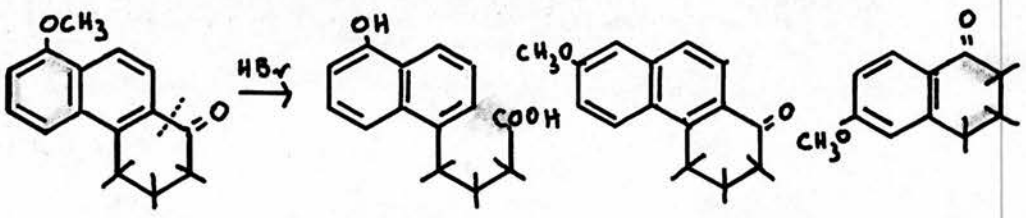


XLIII

The reaction conditions used in this latter case were fairly vigorous, the ketone being refluxed for periods varying between six and twenty-four hours. These conditions ought to have caused fission if it was going to take place, yet only the corresponding phenol was produced in 70 to 80% yield. The work of Buu-Hoi and Cagnaint or Anderson and Thomas[41] in the latter case, may therefore be suspect. The fact that Buu-Hoi and Cagnaint claim that the product, from the Friedel-Crafts reaction between the corresponding cyclopentane acid chloride $C_5H_9(CH_2)_n$ COCl and 2- methoxynaphthalene, is the 2,6- derivative seems doubtful as one would expect the reaction to produce primarily a 1,2- substituted naphthyl ketone. This latter compound would certainly

cleave under the conditions used. This then would seem to be a point in favour of the work of Anderson and Thomas. However steric factors may play an important part in this Friedel-Crafts reaction involving such a long aliphatic chain and so the product may well be that assumed by Buu-Hoi. This still leaves the problem of why it should be decomposed, and not the corresponding phenyl ketone, unanswered. Buu-Hoi gives no details of this particular fission but merely notes that all the ketones he examined underwent the reaction.

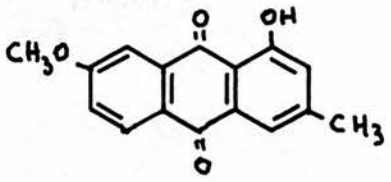
A novel reaction has been reported by Hill, Short and Stromberg[42] in which ring fission of the cyclic ketone (XLIV) took place to give the corresponding demethylated naphthylbutyric acid (XLV) on treatment with an excess of hydrobromic acid in acetic. The shortness of the reaction time ($4\frac{1}{2}$ hours) is particularly interesting.



XLIV XLV XLVI XLVII

This reaction was noticed by chance as these workers set out to demethylate the 1- oxo- 8- methoxy- 1:2:3:4- tetrahydrophenanthrene to the phenol. The corresponding 7- methoxy derivative (XLVI) has been shown to undergo demethylation only (43). Similarly the cyclic ketone (XLVII), 6- methoxy- α- tetralone, demethylates only (44).

In the anthraquinone series Muhlemann[45] found that the methoxyl grouping in 1- hydroxy- 3- methyl- 7- methoxyanthraquinone (XLVIII) does not even demethylate on treatment with this reagent.

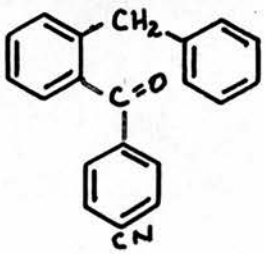


XLVIII

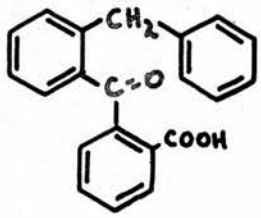
Décombe[46] used hydrobromic acid (48%) with unsaturated cyclic ketones, such as 2- cyclohexene- 1- one, which gives benzene in 60% yield and no ring fission products.

Another interesting use of this acid is in the decarboxylation of carboxylic acids[47]. Several substituted cinammic acids have been decarboxylated and important data regarding the order and mechanism of the reaction have been obtained.

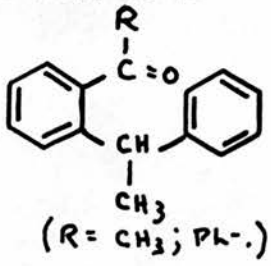
The mixture in glacial acetic acid has also been used with ketones (XLIX), (L), (LI) to give the products (LII), (LIII) and (LIV) respectively, (48), (49), (50).



XLIX

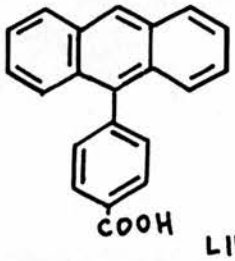


L

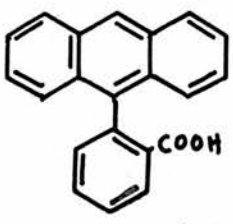


(R = CH_3; Ph-.)

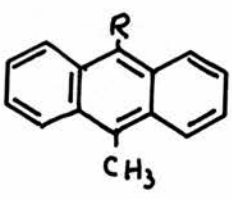
LI



LII



LIII

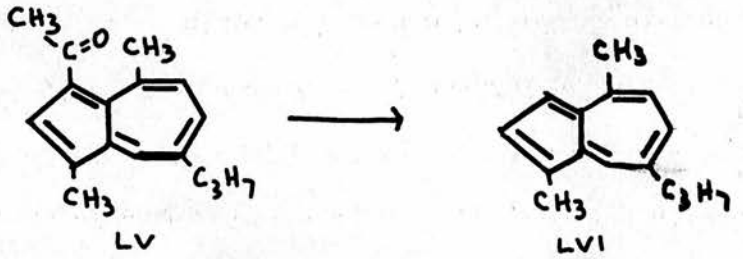


LIV

In those examples, instead of ketonic fission taking place, cyclisation of the ketones to anthracene derivatives has been achieved.

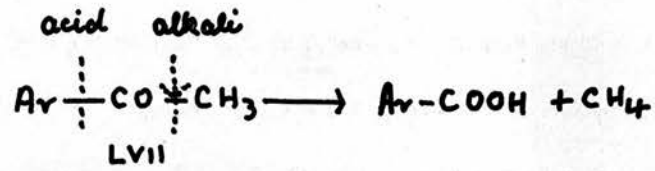
The uses of this hydrobromic acid - glacial acetic acid mixture are wide and varied, demethylation, cyclisation, decarboxylation and ketonic fission all taking place.

An interesting ketonic fission reaction is the cleavage of the ketonic grouping from the guaiazulene nucleus (51). Treatment of 3- acetylguaiazulene (LV) with trichloracetic acid causes a fission of the acetyl grouping to give guaiazulene (LVI). The ready rupture of the carbon-carbon bond is explained by the high electron density associated with the reactive 1-, and 3-, positions in the five membered ring which will render them particularly susceptible to attack by a proton from the acid.



LV LVI

In contrast to the use of acids in this field, a number of workers have tried the effect of alkali on several of the ketones described above. Klages and Lickroth[15], during their work with phosphoric acid, also tried caustic potash. They found a different type of fission taking place.

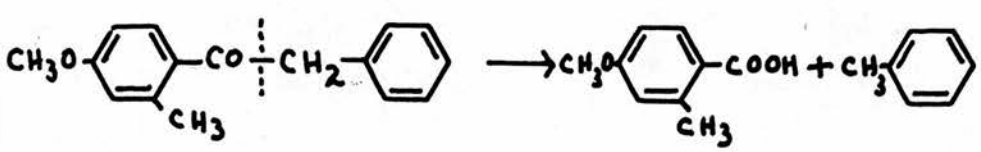


LVII

Considering a ketone such as (LVII) where Ar- is a substituted aromatic nucleus, the ketone behaves as though it was a benzoylated methane and splits as shown to give the corresponding substituted benzoic acid. Fission of such a ketone with phosphoric gave the aromatic hydrocarbon and so the ketone was behaving as an acetylated benzene.

Weiler[19] and Elbs[20] have also investigated the use of alkaline conditions. They used a solution of sodium in amyl or ethyl alcohol as the effective reagent but achieved doubtful results with ketones such as benzoylmesitylene.

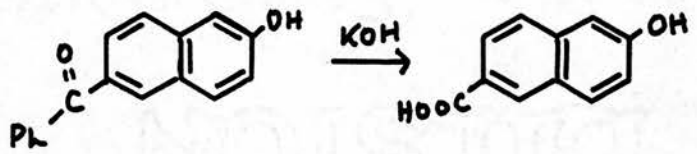
Much later Hill and Short[38] tried the effect of 70% potassium hydroxide on the deoxybenzoins mentioned above (p. 18). Fission took place in a manner similar to that of Klages' work. With 2- methyl- 4- methoxydeoxybenzoin (LVIII) the fission took place between the benzyl nucleus and the carbonyl group instead of at the normal position between the phenyl nucleus and the carbonyl group as found with acid treatment. So the products are 2- methyl- 4- methoxybenzoic acid and toluene.



LVIII

Several other workers (52), (53), (54) used sodamide as the fission reagent. They investigated its action on some unsymmetrical benzophenones containing methoxyl groupings, viz., 2-, 3- and 4- methoxy- benzophenone and 3:4'- dimethoxybenzophenone.

Another example of the use of alkaline conditions is that employed by Schönberg and Mustafa[55] to elucidate the structure of the naphthyl ketone, 6- benzoyl- 2- naphthol (LIX) which gave 6- carboxy- 2- naphthol (LX) on fusion with potassium hydroxide at high temperature. Fission had therefore taken place in the normal way for an alkaline reagent.



LIX LX

From the examples mentioned it is evident that a large number of reagents may bring about the fission of a ketonic grouping from an aromatic nucleus. There are evidently two positions for fission depending on whether the reagent is acid or alkaline. This review is a very broad one and although all the reagents mentioned bring about cleavage, the mechanisms involved may be quite different for different reagents and certainly most of them must be essentially different from that of the Reverse Fries reaction which needs an ortho or para hydroxyl before migration can occur.

Object of Research

In the course of another research by Campbell and Woodham[12] it was noted that 1- benzoyl-β - naphthyl methyl ether, with a boiling mixture of hydrobromic acid and acetic acid, undergoes both demethylation and removal of the benzoyl group to give β - naphthol and benzoic acid. This work is an attempt to discover how general is the reaction and the factors controlling it. In the middle of the research it was found that some investigation of the problem had been carried out by Hill and Short[38]. The results given in this Thesis substantiate and amplify the conclusions of these workers and supply some insight into the mechanism of the reaction. The way is now open for a more detailed investigation of the course of the reaction.

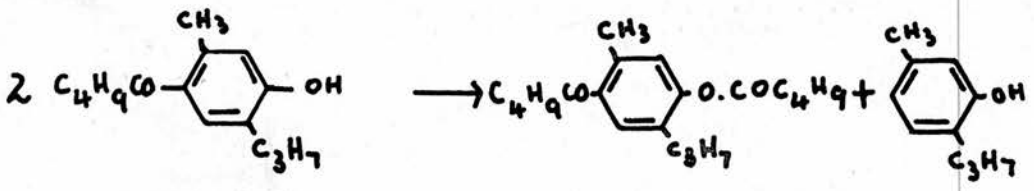
DISCUSSION

1. A General Discussion of Ketonic Fission.

The work of Rosenmund and Schnurr[11] showed that the presence of a phenolic hydroxyl grouping in an aromatic ketone introduced the possibility of a fission of the ketonic group and its subsequent migration to the phenolic oxygen to form the ester. This reaction is a reversal of the Fries Migration.

These workers isolated the ester in many cases. They carried out the reactions at high temperature in the presence of a few drops of an acid catalyst. With a ketone like thymol isobutyl ketone (LXI) they isolated thymol (LXIII), the thymol ester (LXIV), and thymol keto ester (LXII). The migration does not take place through a direct interchange of the ketonic residue - COC_4H_9 with the phenolic hydrogen of the same molecule, but by an exchange involving a second ketone molecule. Thymol and the ketone ester are thus formed:-

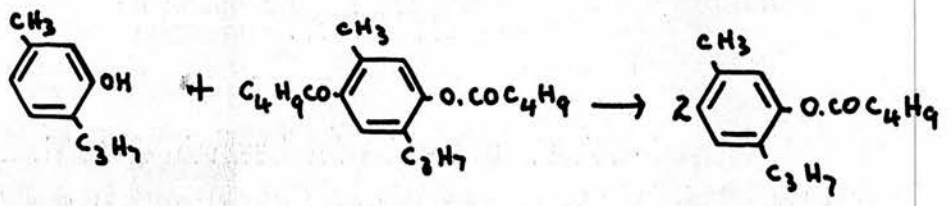
a)



LXI LXII LXIII

Further reaction then takes place between the hydroxyl grouping on the thymol molecule and the ketonic grouping of the keto ester (LXII) to give two molecules of thymol isovalerate (LXIV):-

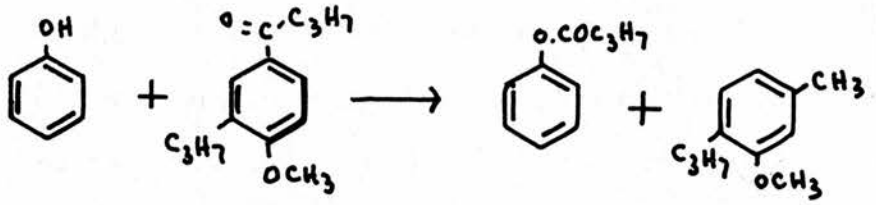
b)



LXIII LXII LXIV

These ideas fit in well with the experimental facts as it was found that during the early stages of the reaction there was a large amount of thymol present and as the reaction proceeded the amount of thymol became smaller. Reaction a) produces thymol but b) removes it again. The concentration of ketone ester is also considerable after a short time but as the reaction nears completion the proportion of ketone ester decreases to zero. On the other hand the percentage of the ester of the phenol increases with time according to equations a) and b).

The ability of the ketone grouping from one molecule to change places with the phenolic hydrogen atom of a second molecule was illustrated by etherification of certain phenolic groupings. Rosenmund and Schnurr used the methyl ether of thymol n- propyl ketone (LXV) and found that no rearrangement between the ketone residue and the methylated phenolic grouping took place. However, when an equivalent amount of phenol was added, it was found that the corresponding ester of phenol (LXVI) and free thymol methyl ether were formed.



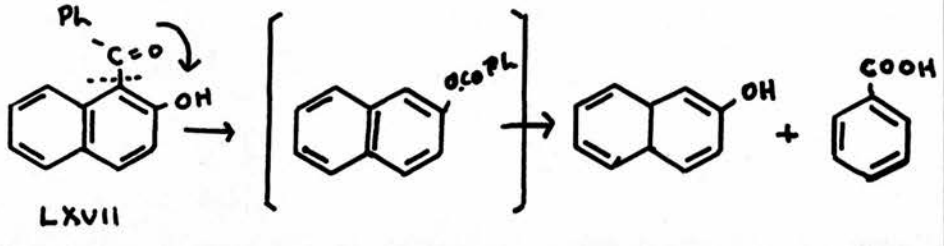
LXV LXVI

The reaction b) (p. 29) was also shown to exist by allowing equivalent amounts of thymol and thymol isobutyl ketone ester (LXII) to undergo the reaction with a longer heating period. Good yields of thymol ester (LXIV) were obtained.

This work gives a very clear picture of the reaction, the experimental results and theoretical ideas agreeing very well and leaving no doubt about the mechanism of the rearrangement. The fact that there was a certain specificity of the reagents able to bring about the reaction was shown by the failure of acids such as nitric, hydrochloric and boric to effect migration.

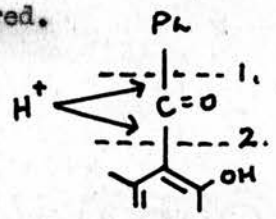
With the use of the hydrobromic acid - glacial acetic acid mixture a similar mechanism might take place. The fission reaction of the ketone grouping in a ketone such as 1- benzoyl- 2- hydroxynaphthalene (LXVII) could occur, as shown, by a migration of the benzoyl grouping to the phenolic oxygen. The resulting intermediate ester would have a short life however, under the conditions of the reaction (a strongly acidic solution at 118 - 120°) and so cannot be isolated. The products are then the corresponding phenol (e.g. β - naphthol) and benzoic acid.

In a reaction such as this the first, and probably the rate determining, step is the fission of the carbon-carbon linkage between the carbonyl grouping and the aromatic nucleus.



LXVII

This bond rupture must be explained both from the standpoint of electronic theory and from that of the activation energy involved in such a break. Both ideas may be correlated satisfactorily. In this work the reaction must be instigated by the attack of a proton H^+, or a solvated proton SH^+, at the bond which has to be ruptured. The attack may take place at positions 1 or 2 with subsequent fission as shown by the dotted line in (LXVII). To distinguish between the two possibilities the effect of the presence of the phenolic grouping in the aromatic nucleus must be considered.



LXVII

First of all however some general remarks will be given on bond rupture by correlating the electronic effect with the modern analysis of activation energy.

To characterise the reactive centres in a compound being attacked and the attacking agent itself, effective charges are schematically given to the reacting species. These charges, according to sign, facilitate or oppose the mutual approach of the two species. They may be modified by the introduction of substituents into the molecule being attacked or by changing the attacking agent. The modification is thought of as an algebraic addition to the repulsion energies and the bond energies involved in the total energy of activation. Considerations on this basis

can lead to predictions of various regularities which assist the interpretation of the experimental facts relating to the influence of substitution on reactivity.

The influence of substituent atoms on the reactivity of organic compounds can be interpreted in an illuminating way by the theory of internal electron displacements of two main types which are called inductive and electromeric. This was advanced by Robinson in a generalised form and later developed by Ingold and Robinson. Its applications to organic chemistry are well known, widely used and accepted.

From a totally different aspect the problem can be investigated from the standpoint of reaction kinetics and, in particular, in terms of activation energy, bond dissociation energies etc.

Although it may seem at first that the two methods of approach are quite different there does exist a definite overlap and it is desirable that their inter-relationships should be stressed. The ideas on reactivity in an organic compound from the electronic viewpoint will be discussed first.

It is widely accepted that the effect of a substituent in an aromatic nucleus will alter the reactivity of the parent compound by altering the availability of electrons at the reactive position. Robinson has divided this electronic effect into two parts which he designates 1) the polar effect and 2) the electromeric effect. The first type deals with compounds in which there is an unequal sharing of the available electrons between atoms. The

latter is closely related to the resonance between the various electronic structures which are possible, with the general ideas of valency still being obeyed.

The effects of a number of substituents in any given reaction normally follows the order predicted from the sign and the size of the induced charges. Deviations from this are explained when a closer analysis of the relative importance of the two effects, polar and electromeric, is carried out.

To obtain some idea of the effect of substituents on the activation energy one must consider a simple system and analyse it to see how the activation energy is made up.

If we consider a compound YZ being attacked by X according to the equation: $X + YZ \longrightarrow XY + Z$ then by the Heitler-London theory YZ will tend to repel X and so X cannot come close enough to YZ to allow reaction to begin. YZ is thus immune from attack. For reaction to begin we must assume that there are two main effects. In the first X is forced against the repulsion of YZ until it is so near that it competes on equal terms with Z which finally splits off and XY is formed. On the other extreme YZ is given so much energy that the bond joining Y and Z is ruptured and so X and Y are free to combine to form XY. It is difficult to decide in any particular reaction which effect is the more important as normally both will play some part in the bond fission. So the activation energy may be considered as being made up of the energy required to overcome the initial repulsion between the approaching reagent and the

energy required to weaken the existing bond between YZ.

Diagramatically then we have:

(i) X Y $\underset{d_1}{\text{———}}$ Z normal state.

(ii) X$\overset{d_2}{\text{----------}}Y\overset{d_3}{\text{----------}}$Z transition state.

The additional charges appearing on atoms as a result of electron displacements produce extra terms in the energy of the bond between the atom and its neighbour.

In such a system one has to consider the repulsion energy which has to be overcome in bringing X up to the distance d_2 of the transition state. There is, in addition, the energy required to stretch the bond in Y — Z from d_1 to d_3. So the activation energy is made up of two parts a) the repulsion energy and b) the bond stretching energy.

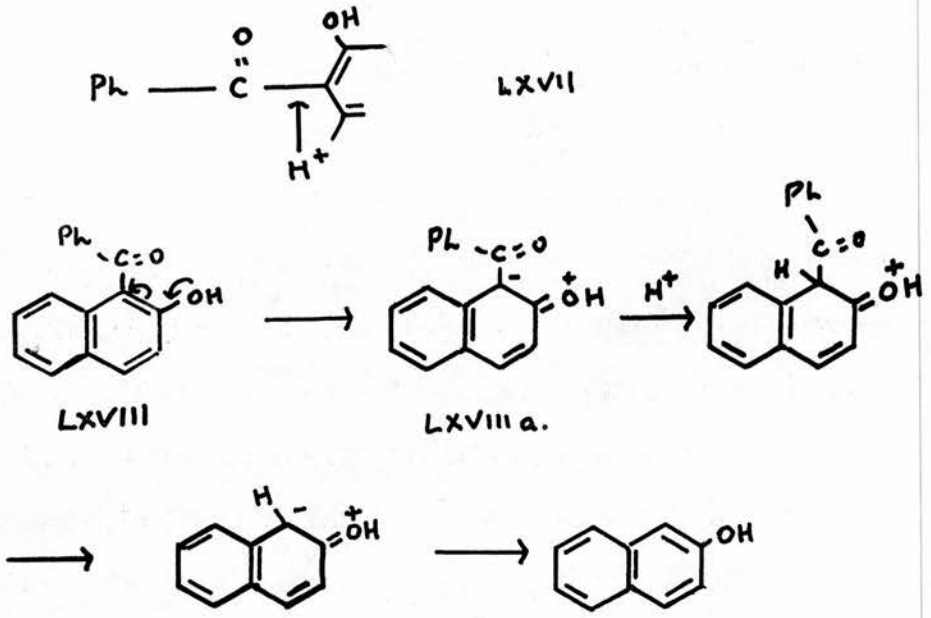
If we consider an electron attracting group, like the nitro, in the Y part of the molecule this will give the carbon atom a slightly positive charge. This charge is added to the charge the carbon atom has in the unsubstituted molecule and so the strength of the bond Y—Z will tend to be increased. Now if X is a positive ion then this positive charge from the nitro grouping will tend to increase the repulsion of the approaching X as well as the bond strength and so the chances of reaction will be decreased considerably.

On the other hand an electron repelling constituent such as a hydroxyl, amino or methyl grouping will have the effect of decreasing the activation energy by means of two effects i) a possible weakening of the bond Y—Z and ii) a decrease in the repulsion energy due to the attraction

between the slightly increased negative charge on the carbon atom at the reactive centre and the positively charged attacking ion X. The difficulty arises as to whether the repulsion energy or the bond stretching energy is the determining factor in a particular case. They are known to vary widely and either may be the important factor. Robinson has said that in benzene substitution reactions the course of the reaction is governed by the ease of approach of a positive or cationoid reagent to a centre of available electrons in the nucleus being attacked. Here the same scheme seems to apply and the repulsion energy factor of the activation energy will be the more important.

The discussion has been restricted to a three centre system with the centres as atoms. This of course need not be and the atoms may be molecular parts which retain their identity during the reaction.

Let us apply this argument to a particular example by returning to the earlier discussion on 1- benzoyl- 2- hydroxynaphthalene. This compound fits in well with the general case mentioned above of a compound containing a hydroxyl grouping which will be electron repelling. The attacking agent is the proton from the hydrobromic acid and the Y—Z bond is that joining the carbonyl side chain to the naphthalene nucleus (LXVII).



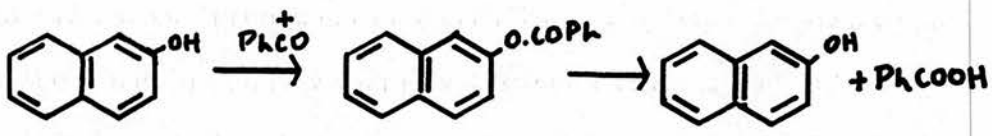
LXVII

LXVIII

LXVIII a.

Considering the influence of the hydroxyl grouping the electromeric effect will be to build up an increased electron density at the α- carbon atom (LXVIII). So this has added a slightly negative charge to the existing charge on the α- carbon atom and there is a slight separation in charge in the molecule as shown in (LXVIIIa). This will facilitate the approach of a proton and in addition have a tendency to weaken the bond which joins the ketonic grouping to the nucleus. If the reduction in activation energy is sufficient then rupture of the bond will take place with the production of particles such as $Ph-\overset{+}{C}=O$ or Ph COBr by reaction with the Br^{-} ions present in the solution. This formation of an acid bromide is not likely in the acidic medium. The other product of the fission is β- naphthol which may be formed by the substitution of the proton from the acid as shown in the reaction sequence above. The possibility of a reaction between the benzoyl

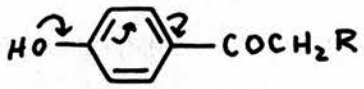
ion $Ph\overset{+}{C}O$ and β - naphthol has been shown to be quite feasible, by the work of Rosenmund and Schnurr (p. 28), with para- hydroxy ketones substituted in the ortho position. In this case the reaction might be represented as:-



As mentioned earlier such an ester would undergo hydrolysis immediately to give benzoic acid and β - naphthol. There is no possibility of this reaction taking place by a Reverse Fries Mechanism however as it has been noted that the Reverse Fries Reaction only occurs if the hydroxyl group is para to the acyl group, and if, and only if, some further substituent in the hydroxy ketone is ortho to the acyl group.

Several other ideas about the mechanism of bond fission in this type of molecule have been advanced. The work of Hill and Short[38] shows general agreement with the ideas expressed above. From their results in the series of deoxybenzoins (p. 18) they were able to draw certain conclusions. They indicate that no fission can take place unless a hydroxyl grouping is present in the phenyl nucleus. The reaction is facilitated by the presence of a grouping such as a methyl but retarded by the electron attracting nitro grouping. The mechanism of the reaction is discussed

generally but there is not sufficient evidence to give any detailed ideas about the mechanism. The authors agree however that at one stage the acceptance of a proton by the α - carbon atom must take place. The influence of the phenolic grouping is one of electromeric change viz.,



Thus a build up of increased electron density takes place as shown. The effect of nitro and methyl groupings is explained as above being due to the general or inductive effect of these groupings.

When a methylated phenolic ketone is used in this reaction no intermediate benzoate can be formed because of the blocking effect of the ether. However with this mixture of hydrobromic acid and glacial acetic demethylation of the ether takes place and the rate of this demethylation is usually quite rapid. Royer and Bisagni[23] have compared the rates of demethylation of several ketones derived from thymol methyl ether. They found that 2- methyl- 4- methoxy- 5- isopropyl methyl, propyl and butyl ketones demethylate readily with pyridine hydrochloride as the effective reagent. An interesting table (part of which is reproduced below) is given showing the change in percentage of demethylated ketone with time.

Table I.

Methyl ketone		Propyl ketone		Butyl ketone	
Reaction time (mins.)	Yield of phenolic ketone (%)	Reaction time (mins.)	Yield of phenolic ketone (%)	Reaction time (mins.)	Yield of phenolic ketone (%)
15	41.5	15	28.5	15	11.0
25	56.5	30	43.0	37	28.0
32	64.5	37	60.0	41	40.0
50	72.5	45	46.5	45	29.5
55	74.0	55	28.0		
60	75.0				
70	54.0				

These rates cannot be compared on a quantitative basis as the reaction temperatures are different in each case. However it is evident that in all three cases demethylation is relatively fast reaching a maximum after 40 to 50 minutes. Thereafter the yield of phenolic ketone starts to fall. This is due to the increasing importance of the second reaction which is that of ketonic fission. If the yield of phenolic ketone is plotted against time then a curve of the type shown in Fig. I is obtained with a sharp maximum appearing during the early stages of the reaction.

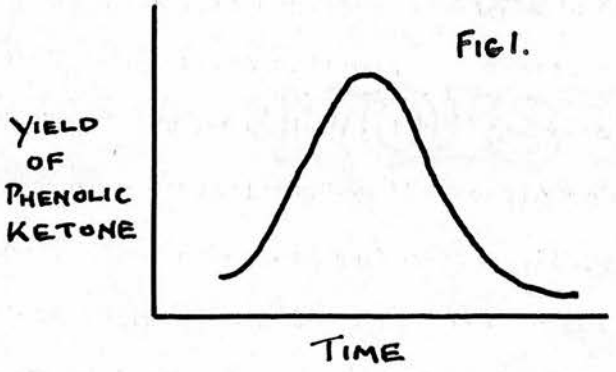


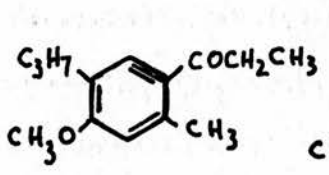
FIG I.

It is difficult to decide from these results whether fission is taking place at the same time as demethylation or whether it follows as a result of demethylation. If we consider the methyl ketone in Table I it is seen that there is a steady increase in the yield of demethylated ketone until a maximum of 75% is reached. This figure is quite high and it indicates that, up to this stage (60 minutes reaction time), the main reaction taking place is that of demethylation. From general considerations demethylation will be easier

to accomplish than the bond rupture necessary for ketonic fission. Certainly the fission reaction does not become important in this case until a large amount of demethylated ketone is present in the reaction medium and so the necessity for the presence of a hydroxyl grouping is strongly indicated.

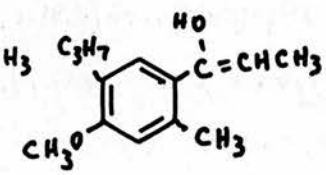
So these results could lend themselves to a ready explanation of the fission taking place by the re-arrangement idea of Rosenmund and Schnurr. On the other hand the hydroxyl may act solely as an electron repelling group to build up the necessary electron density. The precise kinetics of such a reaction as this, involving both demethylation and fission, would be very difficult to investigate and until some work of this nature is carried out no definite conclusions can be drawn.

Royer and other workers[24] have suggested three other interesting possibilities and methods of fission of the ketonic grouping in the ketones studied. The idea put forward is that a ketone such as thymol propyl ketone (LXIX a) for example may exist in both a ketonic and enolic form.



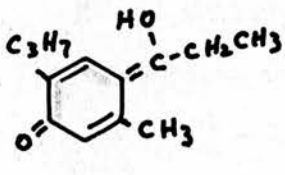
LXIX

a) keto



LXIX

b) enol



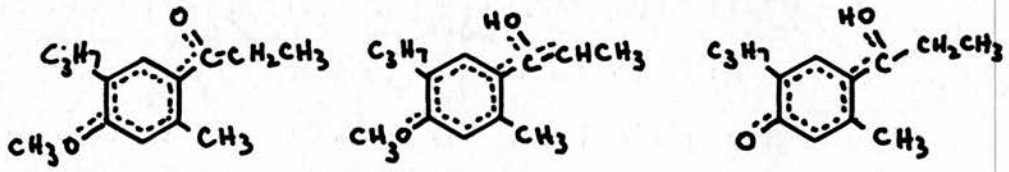
LXIX

c) quinonoid

On the other hand the possibility of a quinonoid form arises with a hydroxy ketone such as LXIX c.

Hill and Short[38] also noted the possibility of such forms and suggested they might play some part in the fission reaction. Such structures would alter the strengths of the bonds which are being attacked and at first sight the new structures would appear to facilitate the fission process especially the quinonoid form (LXIX c) with its reactive ethylinic linkage.

To obtain definite information of the effect of this tautomerism the dissociation energies associated with each type a) b) and c) i.e. the dissociation energies with regard to the bonds joining the carbonyl group to the aromatic nucleus must be measured and their relative ease of fission compared. The resonating structures for each form may be written as a') b') and c').



a') b') c')

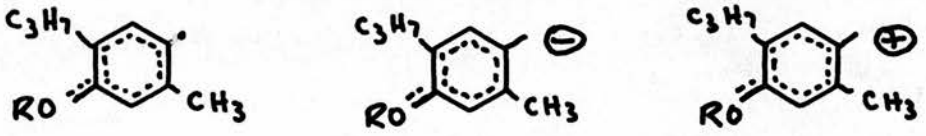
The calculation of the bond dissociation energies by the French workers was carried out according to the Linear Combination of Molecular Orbitals Theory assuming that the energy associated with the σ bond for each form is more or less constant. This seems to be a reasonable assumption. On the other hand the energy associated with the π bond will vary considerably for the three different structures.

The energies involved have been calculated for each form when the fission process takes place by the following methods:

i) a homolytic process,

ii) a heterolytic process with an anion involving the aromatic nucleus,

iii) a heterolytic process with a cation involving the aromatic nucleus.



i.) ii.) iii.)

R = -H or $-CH_3$

The homolytic process is most unlikely especially in the acid conditions of the reaction medium. The heterolytic processes are much more feasible in such a medium as they are brought about by the interactions of ions of the polarised molecules.

So, ruling out the homolytic process, the form with the lowest dissociation energy was found to be form c) i.e. the quinonoid type of molecule, splitting by method iii).

The demethylation process which would thus lead to the possibility of the formation of form c) gives a structure which is easily cleaved by the heterolytic process. It is quite probable therefore that the fission reaction does

not become important until the appearance of demethylated ketone in the reaction mixture takes place allowing a structural rearrangement to this quinonoid form. This theory supports the experimental facts quite well and it seems much more feasible than the rearrangement reaction discussed earlier.

The work by the French workers then suggests the possibility of a quinonoid form of the ketones which will be fairly easily cleaved. The deciding factor as to whether this form is actually present or not is the problem of whether the fission reaction can take place while the compounds are present solely as the methyl ethers or whether a primary demethylation must take place before the fission reaction is possible. From this the idea of an intermediate rearrangement via the substituted phenyl ester is unlikely, e.g., the fission of 1- benzoyl- 2- hydroxy naphthalene via β- naphthyl benzoate.

The relative strengths of the reagents used and the reaction temperatures merit some consideration in this work because the fission can also take place with ketones which have no phenolic grouping if the conditions are sufficiently severe. Klages[15], for example, was able to split off ketonic residues from an aromatic nucleus by using boiling syrupy phosphoric acid. This however is an example of fission under extreme conditions.

No examples of ketonic fission have been reported with hydrobromic acid in glacial acetic acid unless there is

a hydroxyl grouping present in the nucleus. This is a good indication that the presence of such a hydroxyl is a necessity to lower the activation energy of the bond which has to be ruptured.

The French workers' idea of the mechanism is suspect in some ways. In particular the idea of a fission process involving a positively charged aromatic nucleus as in iii) above seems quite wrong. It is not at all clear how fission of such a polar structure could take place by the attack of a proton. Their idea of an easily cleaved intermediate quinonoid form can be easily tested by discovering whether the methoxy ketone can undergo fission without demethylation. Some examples in the present work (p. 77) show that fission can take place without demethylation.

Although the work of Royer and co-workers suggests that demethylation takes place before ketonic fission can occur the effect may simply be due to the greater electron donating power of the hydroxyl grouping. In fact the results of this work can be accommodated simply as an example of the more general theory of proton attack at a negative centre.

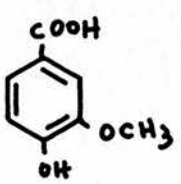
The present work substantiates the fact that the ketonic fission reaction takes place by the attack of a proton at the carbon atom which has been made reactive due to the electronic effect (mesomeric or inductive) of substituents in the nucleus. The other effects such as

bond repulsion energies, weakening of the bond which is to be ruptured etc., may also play some part in the fission mechanism but are less important.

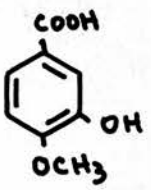
2. Relationship between Ketonic Fission and the Decarboxylation of Substituted Aromatic Acids.

It has been stated in the introduction that several workers have noticed the effect of substituents on the decarboxylation of aromatic acids. Cazeneuve (56) has provided some early semi-quantitative results which illustrate the effect of substituents on the ease of decarboxylation. He found that the greater the number of hydroxyls present the more easily was carbon dioxide lost. From his results a list, in order of increasing ease of decarboxylation may be made viz., benzoic < salicylic(240°) < protocatechuic (3:4- dihydroxybenzoic) (180°) < gallic (3:4:5- trihydroxy-) (115°). The figures in brackets give the decarboxylation temperatures in aniline as solvent. From this he noted the importance of the position of the hydroxyls, the order of effectiveness being o > p > m.

An interesting example given is the case of vanillic acid (3- methoxy- 4- hydroxybenzoic acid) (LXX) and the isomeric 3- hydroxy- 4- methoxybenzoic acid (LXXI). The former was found to undergo decarboxylation in contrast to the latter. So the methoxyl grouping would appear to play no part in the reaction.



LXX



LXXI

In the naphthalene series α - and β - naphthoic acids were quite stable in aniline but the corresponding 1,2-hydroxynaphthoic acids lost carbon dioxide readily. The

1,3- acid was however quite stable under similar conditions.

These results show the importance of the position of the hydroxyl which is influencing the ease of removal of carbon dioxide by an electromeric shift in the same way as has been described for the ketonic fission reaction.

Brown, Hammick and co-workers[57] studied the rate of decarboxylation of several hydroxybenzoic acids in resorcinol solution. They showed that for salicylic, 2:4- dihydroxy- and 2:4:6- trihydroxybenzoic acids there was a fall in activation energy i.e. an increase in rate, with an increase in ortho and para substitution by the hydroxyl groupings. This is further support for the view that the reaction takes place by the approach of a proton to the α - carbon atom, the electron density of which will be enhanced by the hydroxyl groupings. Such acids should be stable in alkaline conditions and this was found to be so.

The meta- hydroxybenzoic acids such as (LXXI)above in which the hydroxyl cannot make any appreciable contribution to the electron density on the α - carbon are found to be quite stable in acid solution.

Fieser and Fieser[58] have also suggested that this decarboxylation reaction may occur by the attack of a proton on the negative α - carbon atom.

This evidence lends support to the ideas put forward for the ketonic fission reaction. A great deal of work has been carried out by Brown, Hammick and other workers in an attempt to obtain some idea of the exact reaction

kinetics of the decarboxylation mechanism. This will be discussed in detail when the results from the section of quantitative work are described and again a strong correlation between the two reactions, decarboxylation and ketonic fission, will be shown.

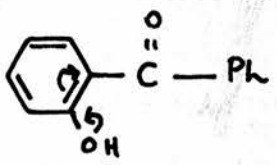
3. Discussion of the Experimental Section.

With the general considerations of the preceding discussion in mind several hydroxy and related ketones were synthesised and allowed to undergo the fission reaction. The ketones may be broadly grouped and discussed according to the type of aromatic nucleus present: benzene, hydrindene, naphthalene and phenanthrene.

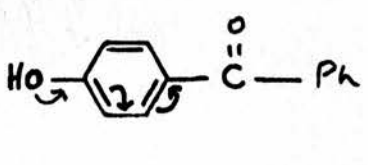
SECTION I.

Benzene Series

The simplest hydroxy ketone in this series, o-hydroxybenzophenone, did not undergo the fission reaction. p- Hydroxybenzophenone was not expected to give fission products either because, if there is not sufficient reduction in the activation energy of the appropriate bond in the ortho ketone (which should have a considerable electromeric effect at the α - carbon atom), no reaction can be expected with the para isomer. This follows from the fact that the electromeric effect in the latter case has to be relayed a greater distance in the benzene nucleus and must necessarily be less intense than that due to the adjacent hydroxyl in the ortho position (LXII) and (LXXIII). No fission was obtained with p- hydroxybenzophenone.



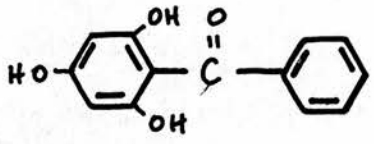
LXXII



LXXIII

Following from this, 2:4- dihydroxybenzophenone suggested itself as an interesting ketone to investigate. However, like the monohydroxy ketones, it was found to give no fission products although the effects of the two hydroxyl groupings must combine to give a greater increase in electron density at the α- carbon atom. Presumably then the combined effect is not of sufficient magnitude to allow cleavage.

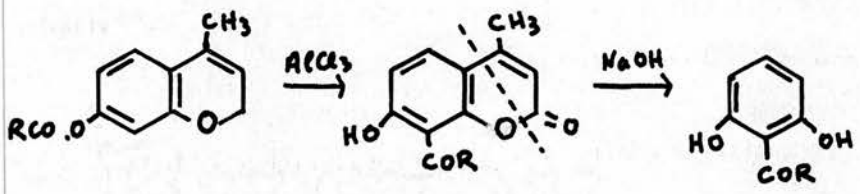
Benzoylphloroglucinol (LXXIV) was cleaved readily. In this ketone the hydroxyls are all ortho and para to the reaction centre and so the combined electromeric effect has reduced the activation energy of the carbon-carbon bond sufficiently to allow heterolytic fission to take place.



LXXIV

After a reaction time of seven hours the yields of phloroglucinol obtained were about 40%. After sixteen hours this had risen to over 70%. In both cases the phenol produced was estimated by weighing the complex which phloroglucinol forms with furfural. Good quantitative results were obtained. The yields of the phenol, calculated by this method, were higher than the corresponding yields of the other fission product benzoic acid, which were obtained by direct weighing, doubtless due to the failure to extract all the acid.

Obviously the next ketone to investigate was 2:6-dihydroxybenzophenone. The synthesis of this compound was attempted using an intermediate coumarin derivative as the starting material. The rearrangement of the benzoate of 4- methyl- 7- hydroxycoumarin (LXXV ; R = C_6H_5) was attempted according to the method of Baker[59] by a Fries Reaction.



LXXV LXXVI LXXVII

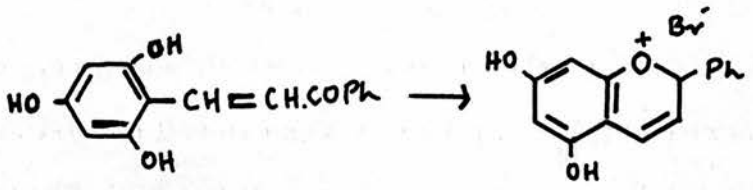
However failure to isolate any 4- methyl- 7- hydroxy- 8-benzoylcoumarin (LXXVI; R = C_6H_5) from the aluminium chloride treatment necessitated the abandonment of this synthesis. Instead the corresponding methyl ketone (LXXVI ; R = CH_3) was prepared in the same way in reasonable yield. The ketone (LXXVI) was treated with alkali to break open the heterocyclic ring as shown by the dotted line in (LXXVI) giving 2:6- dihydroxyacetophenone (LXXVII). The failure of the first Fries Reaction is another example of benzoates being much more difficult to rearrange than the corresponding acetates.

The methyl ketone was treated in the usual way and after seven hours a yield of 75% resorcinol was obtained. Three hours yielded 80% of the phenol, so the fission reaction is nearly complete even after three hours treatment.

The presence of the di-ortho substituents seems to exert a strong influence on the fission, an influence as strong as the trisubstituted nucleus in benzoylphloroglucinol. This suggests that the p- hydroxyl group in the latter plays only a small part in the reaction.

As expected the unsymmetrical 2:3:4- trihydroxybenzophenone showed no fission reaction and the ketone was quantitatively recovered. Therefore the hydroxyl in the meta position contributes very little to the electron density at the α - carbon atom.

The unsaturated analogue of benzoylphloroglucinol, 2:4:6- trihydroxychalkone (LXXVIII) was synthesised by condensing acetophenone with phloroglucinol aldehyde in alcoholic potassium hydroxide. It was allowed to undergo the fission treatment but no fission products could be identified. Instead an addition complex of some kind was formed between the chalkone and hydrobromic acid. This was shown, by analysis, to have the empirical formula corresponding to one molecule of acid and one of the chalkone. The experiment was thus abortive but the discussion will be continued when several chalkones in the naphthalene series are considered. The compound which has been formed is almost certainly 5:7- dihydroxyflavylium bromide (LXXIX) by cyclisation of the chalkone. Johnson and Melhuish [60] report the synthesis of the corresponding chloride which has a high melting point ($>250^{\circ}$) [the bromide decomposed above 300°].

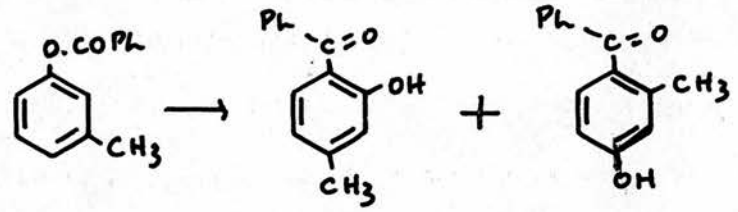


LXXVIII LXXIX

The effect of hydroxyl groupings on the ease of fission having been demonstrated, the next step was to investigate what effect alkyl groupings have on the fission process when included in the same nucleus as the hydroxyl.

Most of the alkyl substituted ketones investigated were synthesised by the Fries Reaction on the corresponding xylenol acetates or benzoates.

The first pair of this type were prepared simultaneously by a Fries treatment of m-cresol benzoate (LXXX), with aluminium chloride in the absence of solvent.



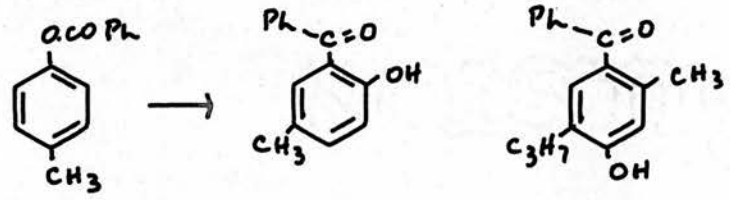
LXXX LXXXI LXXXII

The resulting mixture of the two isomeric ketones 2-hydroxy- 4- methylbenzophenone (LXXXI) and 2- methyl- 4-hydroxybenzophenone (LXXXII) were separated very effectively by trituration with methanol. Steam distillation as a method of separation proved a tedious and nearly fruitless method as only a very small amount of the o- hydroxy isomer was obtained in the distillate.

Both these ketones were allowed to undergo the reaction with somewhat similar results. After seven hours the

presence of benzoic acid could not be detected in either case. Under the more prolonged conditions of a twenty-four hour reflux time a little acidic material was obtained. 2- Hydroxy- 4- methylbenzophenone gave 14% and the other isomer 23% of benzoic acid.

So the combination of the methyl and hydroxyl groupings is providing a sufficiently large electronic effect for a split of the carbon-carbon bond only when the reaction is prolonged for twenty-four hours. The isomeric 2-hydroxy- 5- methylbenzophenone (LXXXIII) from p- cresol benzoate was expected to give no evidence of cleavage products even after twenty-four hours. This was found to be so and a quantitative yield of the starting ketone was recovered.

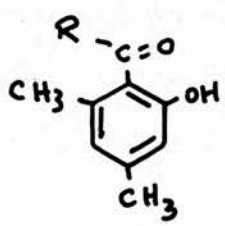


LXXXIII LXXXIV

The shift of the methyl grouping from the 4- to the 5- position has sufficiently reduced the inductive effect to prevent a successful attack at the α - carbon atom in the benzene nucleus. In the ortho and para di-substituted ketones (LXXXI) and (LXXXII) the electronic effects due to each grouping reinforce each other whereas here the effect of the methyl group in a meta position to the reactive centre will have little or no effect on the electron density at this carbon atom and so the ketone behaves in an analogous manner to o- hydroxybenzophenone.

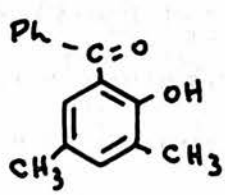
Royer et al.[23] have shown that ketones formed from thymol and its methyl ether undergo this decomposition when treated with pyridine hydrochloride. Benzoylthymol (LXXXIV) was found to undergo cleavage with the hydrobromic acid - glacial acetic mixture after seven hours treatment, benzoic acid being obtained in a 22% yield. When this result is compared with the yield of acid from 2- methyl-4- hydroxybenzophenone above one finds that the latter gave no fission product after seven hours and so the effect of the strongly electron repelling isopropyl grouping in the 5- position seems quite considerable and instead of having a deactivating effect actually adds to the negative charge on the α - carbon atom. The possibility of fission of this type of ketone taking place by the formation of the quinonoid form or by the rearrangement of the benzoyl grouping via the intermediate ester have already been discussed in some detail (p. 38).

The effect of two methyl groupings in the aromatic nucleus containing a hydroxyl is shown by 2- hydroxy-4:6- dimethylacetophenone and the corresponding phenylketone (LXXXV) which have all the substituents in the symmetrical ortho and para positions.



(R= CH_3; C_6H_5.)

LXXXV



LXXXVI

The phenyl ketone (R = C_6H_5) gave a 78% yield of benzoic acid and 72% of 3:5- xylene- 1- ol after twenty-four hours thus showing the effect of the symmetrical substitution in the nucleus. Benzoylphloroglucinol showed that fission had proceeded to the extent of 70 - 80% after sixteen hours. So the influence of the methyl groupings is slightly less than that of the hydroxyls as is expected from the work on aromatic substitution involving these radicals. The methyl ketone (R = CH_3) gave a 54% yield of 3:5- xylene- 1- ol on similar treatment indicating that the phenyl ketone cleaves more readily as a result of the completely conjugated substituted benzophenone in this case. Seven hour treatments of these ketones gave no fission products.

Both these ketones were prepared from the corresponding esters of 3:5- xylene- 1- ol by treatment with one molecule of catalyst. As mentioned earlier (p. 2) the use of more than one molecule of catalyst results in a rearrangement of the methyl groupings. In the Fries Reaction on the acetyl derivative of 3:5- xylene- 1- ol with one molecule of aluminium chloride it was found that distillation of the resulting oil produced a main fraction which was the required ketone (LXXXV ; R = CH_3). A higher boiling fraction yielded a pale yellow solid which analysed well for a similar ketone with only one methyl group in the nucleus. It would therefore appear that one of the methyl groups has been split off from the nucleus during the reaction.

Bad delay's work.

The unsymmetrical 2- hydroxy- 3:5- dimethylbenzophenone

(LXXXVI) showed no signs of fission after seven hours but unexpectedly cleaved to the extent of 10% after twenty-four hours.

The methyl groups meta to the reactive centre have thus an appreciable effect on the electron density at that point and a comparison may be drawn between this ketone, 2- hydroxy- 5- methylbenzophenone and 2- hydroxy- 4- methylbenzophenone. The former gave no fission products but the latter decomposed to the extent of 14%. So the two methyl groupings in the 3- and 5- positions have an effect slightly less than that of a single methyl in the 4- position. On the other hand 4- hydroxy- 3:5- dimethylbenzophenone was recovered quantitatively after twenty-four hours indicating that the o- hydroxyketone is more susceptible to fission than the corresponding para derivative. This indicates that the effect of an adjacent hydroxyl is greater than that of the more distant para grouping.

It was thought that benzoylmesitylene, 2:4:6- trimethylbenzophenone, would be an interesting ketone to investigate. Many workers have subjected it to various reagents and fission products have often been identified. From the ketones already discussed it is evident that this symmetrical trimethyl compound ought to have a sufficiently large inductive effect at the α - carbon atom to produce fission with hydrobromic acid in glacial acetic. However seven and twenty-four hour treatments showed no evidence of fission. The longer reflux period should have been sufficient to produce fission when one remembers that 2-

hydroxy- 4:6- dimethylbenzophenone suffered 70 - 80% decomposition in this time.

This shows that the presence of at least one hydroxyl group is essential if ketonic fission is to occur and that methyl groupings alone are not sufficient.

From the ketones discussed in this section three main points are evident:-

i) A hydroxyl grouping is necessary in either an ortho or para position in the nucleus before fission occurs.

ii) The presence of a methyl grouping enhances the fission reaction, particularly if it is in an ortho or para position.

iii) The fission reaction is probably most satisfactorily explained from the general theory of proton attack.

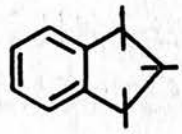
DISCUSSION

SECTION II.

Hydrindene Series

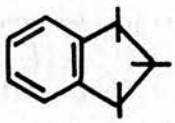
pp 110, 116

Mills and Nixon reasoned that a five membered ring could only be fused to a benzene ring if the two rings possessed a single bond in common. Otherwise there would be a considerable distortion of the valency angles.



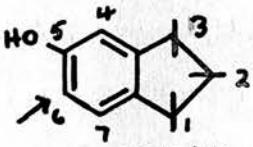
LXXXVIIa.

(unstrained)



LXXXVIIb.

(strained)

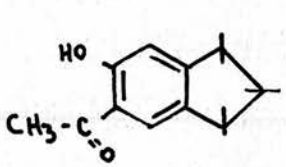


LXXXVIII

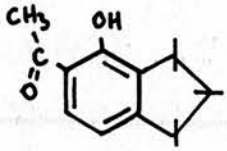
They said that the overall effect would be to stabilise or fix the double bonds in the hydrindene molecule as in (LXXXVIIa). Mills and Nixon tested these predictions by investigating the products of diazo-coupling and bromination of 5- hydroxyhydrindene (LXXXVIII) the reactions taking place at the 6- position. In contrast however other workers such as Springall[61], Berthier and Pullman[62] and Baker[63] have produced considerable evidence, both practical and theoretical to show that the Mills-Nixon Hypothesis is no longer tenable and that the central carbon-carbon bond differs little from that of an ordinary aromatic bond.

The present work substantiates the conclusions of Baker and others that there is no bond fixation in the aromatic ring of the hydrindene molecule.

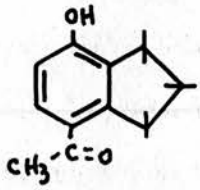
All the ketones in the present work were synthesised by the Fries Reaction. The first compound was 5- hydroxy- 6- acetylhydrindene (LXXXIXa).



LXXXIX

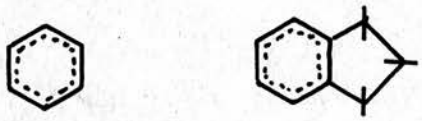


XC



XCI

This ketone gave a 50% yield of 5- hydroxyhydrindene after boiling with the hydrobromic acid - glacial acetic acid mixture for seven hours. If the Mills-Nixon Effect is correct this is to be expected as the bond joining C_5 and C_6 will then be a double bond. However the substance also resembles 2- hydroxy- 4:6- dimethylacetophenone which has been shown to undergo fission to the extent of 54% (p. 57). It would appear that the hydrindene nucleus is very similar to that of the resonating benzene system with little or no bond fixation present viz.,

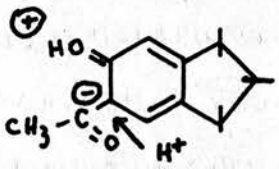


The aromatic ring in hydrindene may be thought of as containing a resonating system of mobile π electrons like the simpler benzene ring.

The phenyl ketone corresponding to this methyl ketone (LXXXIXa) was found to give much smaller yields of the phenol even after twenty-four hours treatment. The reason for this is not quite clear but it strengthens the evidence against the double bond character of the C_5 - C_6 bond.

The ketones, 4- hydroxy- 5- acetylhydrindene (XC) and 4- hydroxy- 7- acetylhydrindene (XCI) were synthesised by the Fries Reaction on the acetyl derivative of 4- hydroxyhydrindene. The reaction gave a mixture of both which was separated by trituration with methanol. These ketones underwent fission to the extent of 70% and 50% respectively. The yields of 4- hydroxyhydrindene recovered were determined by converting the low melting phenol to the aryloxyacetic acid derivative and calculating the yield of phenol in the light of the results obtained by similar treatment of known weights of pure 4- hydroxyhydrindene.

The fact that fission took place with all three ketones precludes the existence of bond fixation in the hydrindene molecule. If such a fixation did exist then 4- hydroxy- 5- acetylhydrindene would show no evidence of decomposition. This agrees with the idea of a resonating system of electrons in the aromatic ring of the hydrindene molecule which allows the eledtromeric effect to occur to give a rearrangement to the polar structure (LXXXIXb).



LXXXIXb

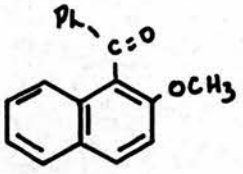
This transition complex will then be attacked at the negative centre by a proton from the acid medium thus bringing about a fission of the ketonic grouping from the nucleus. This work thus agrees with the results of Baker and others in that it provides evidence against any fixation of the bonds in the hydrindene molecule.

There is however an additional feature which must be mentioned. If the 4:5- ketone is considered as an alkyl substituted benzene like 2- hydroxy- 3:4- dimethylacetophenone then the latter would be expected to give only a very small yield of fission product (cf. 2- hydroxy- 4- methylbenzophenone(p. 55) which gave only 14% benzoic acid on prolonged treatment). The high yield of fission product from the hydrindene derivative must be explained by a difference of some kind between the benzene and hydrindene nuclei.

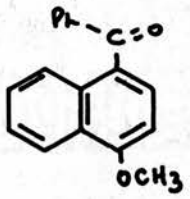
SECTION III

Naphthalene Series.

The simplest hydroxyketone of this series is 1- benzoyl- 2- hydroxynaphthalene. This ketone has been investigated thoroughly and a detailed discussion is given in the section dealing with quantitative work on the reaction. A large scale fission reaction produced yields of β- naphthol of 70 - 80% after seven hours treatment.



XCII



XCIII

The corresponding methyl ether (XCII) which Woodham tried to demethylate[12] was found to suffer a similar decomposition in the same time.

So the heavier aromatic nucleus with the possibility of increased conjugation and greater double bond character of some bonds needs the presence of only one hydroxyl grouping to allow fission to take place in contrast to the three such groupings (or two di-ortho groupings) necessary in the benzene nucleus.

The reaction with 1- acetyl- 2- hydroxynaphthalene also gave fission but the yield of phenol was slightly smaller (68%).

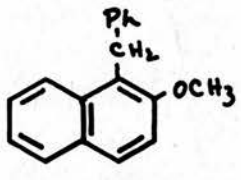
The p- substituted ketone 1- benzoyl- 4- methoxynaphthalene (XCIII) showed a similar decomposition under the same conditions the rate of fission being slightly less than that of the ortho-ketone, as expected. Buu-Hoi[39] predicted that this ketone would show no fission properties. The yield of β - naphthol was 60%.

Woodham (loc. cit.) tried the effect of the reagent mixture on 1- benzoylnaphthalene and found that no decomposition took place.

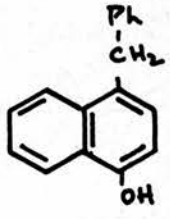
Clemmensen reduction of the 1,2- and 1,4- phenylketones above gave 1- benzyl- 2- methoxy- and 1- benzyl- 4- hydroxynaphthalene respectively (XCIV) and (XCV).

It is noteworthy that although demethylation accompanied the reduction of the 1,4- ketone none was found with the 1,2- derivative.

Both these reduced compounds showed no fission of the benzyl substituent. Demethylation of 1- benzyl- 2- methoxynaphthalene occurred.



XCIV



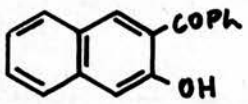
XCV

Therefore the presence of the carbonyl group is all important in the fission. With the phenyl ketones it allows the whole molecule to exist in a conjugated form. Reduction to the benzyl side chain destroys the conjugation between the naphthalene and the carbonyl group, and so it appears that for fission two factors are operative,

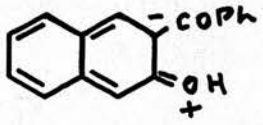
a) an electromeric effect of the hydroxyl group and

b) some other factor at present unknown due to the presence of the carbonyl group.

The next ketone to be investigated was the 2,3-substituted ketone, 2- benzoyl- 3- hydroxynaphthalene (XCVIa) which was synthesised by a Friedel-Crafts reaction between the acid chloride of 2- methoxy- 3- naphthoic acid and benzene, demethylation of the ether taking place during the reaction. Twenty-four hours treatment of this ketone under reflux produced no decomposition.

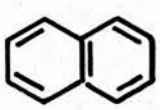


XCVIa.

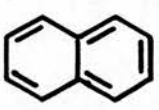


XCVIb.

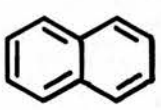
Now in the naphthalene molecule the bond structure is normally written as in (XCVIIa) which allows both rings to be fully aromatic. Structures (XCVIIb) and (XCVIIc) are also contributing forms and they will play a minor role in the resonance hybrid.



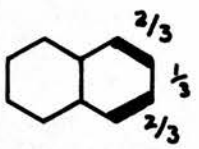
XCVIIa.



XCVIIb.



XCVIIc.

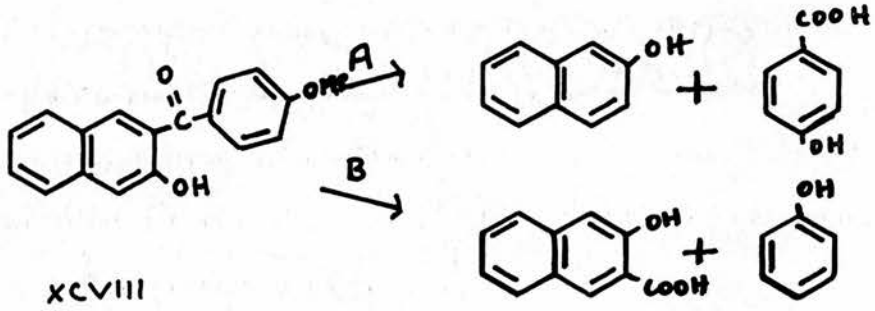


XCVIId.

It is generally accepted that the 1,2- bond is nearly a double bond and shows at least "$\frac{2}{3}$ double bond" character,

whereas the 2,3- bond has only "⅓ double bond" character (XCVIId). Proof of this had been obtained from X-ray work on the lengths of the bonds. So this 2,3- substituted ketone will not show the normal conjugation effect between the hydroxyl and the adjacent benzoyl grouping. For fission to take place a rearrangement to the di-quinonoid structure (XCVIb) would have to take place. The existence of such a high energy structure is extremely unlikely.

In an attempt to lower the activation energy of the bond the corresponding p- methoxybenzoyl ketone (XCVIII) was synthesised by a similar Friedel-Crafts reaction using anisole with the acid chloride. The influence of the methoxyl in the benzene ring gave an increased yield of the ketone.



XCVIII

This ketone may split in to ways (A or B).

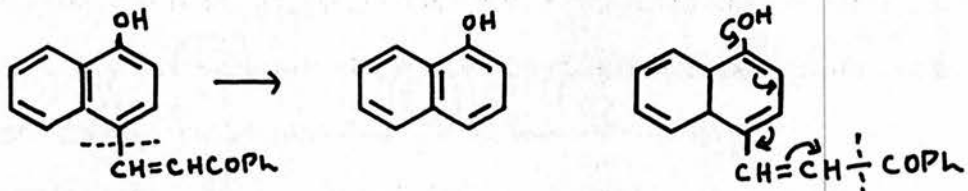
The ketone was treated under reflux for seven hours and a little acidic material was obtained by extraction with sodium carbonate, but a slight depression in the mixed melting point determination, with 2- hydroxy- 3-naphthoic acid, was found. An 80% recovery of the original ketone was obtained. After twenty-four hours a similar

sodium carbonate soluble solid was recovered which however gave a 2:4- dinitrophenylhydrazone suggesting it was demethylated starting ketone. To establish this definitely several paper chromatograms were run to find if any 2- hydroxy- 3- naphthoic acid was present in the acidic solid obtained from the fission treatment. (The melting point of this impure material recovered was about 15° lower than that of the naphthoic acid.) The solvent used in the chromatograms was a two-phase saturated sodium chloride- n- butanol- pyridine mixture and the papers were run for twenty-four hours by capillary ascent. The solid from the reaction was run alongside blanks of phenol, 2- hydroxy- 3- naphthoic acid and the starting ketone as well as a mixture of all three. Good separation of the acid and the ketone was obtained from the mixture, the spots being identified in ultra-violet light. Phenol did not show up under this however. No separation was obtained with the unknown solid and no spot corresponding to the position of the 2- hydroxy- 3- naphthoic acid spot in the blank could be seen. So this established the absence of the acid in the product from the reaction. Evidently no fission had taken place, the ketone being demethylated only. The solubility in sodium carbonate is explained by the presence of the second hydroxyl grouping after demethylation.

In the benzene series the vinyl ketone 2:4:6- trihydroxy- chalkone has been tried but because of the hydrobromic acid complex formed no fission took place. It was decided to try a vinyl ketone of this type in the naphthalene series. 1-

Hydroxy- 4- naphthylideneacetophenone (XCIX a) was readily synthesised by a condensation between 4- hydroxy- α - naphthaldehyde and acetophenone in alcoholic caustic potash solution. The resulting unsaturated ketone gave the expected dinitrophenylhydrazone.

Hydrobromic acid treatment of the ketone yielded 14% of α - naphthol showing that fission had taken place. No acidic material was recovered but a purple glistening platy solid, insoluble in ether but soluble in chloroform, was produced. This compound may be a polymer formed from the unsaturated side chain which has been split off. The fact that α - naphthol has been produced means that the split has taken place at the bond joining the side chain to the nucleus.



XCIX a. XCIX b.

The nature of the purple solid is not important but the identification of the phenol shows that the conjugated side chain has reacted in the same way as the simpler benzoyl grouping although the possibility of the electromeric effect being relayed via the unsaturated grouping to the bond joining the benzoyl group to the unsaturated bond, as shown in (XCIX b), was not forgotten. The fact that the split took place at the normal position shows that the build up of the electron density is still at the α - carbon atom in

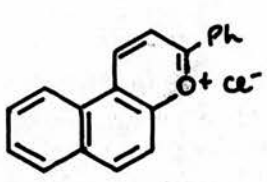
the naphthalene nucleus. It must be pointed out that this fission reaction has taken place with some difficulty. The fact that fission has taken place with this ketone shows

i) the electromeric effect is all important

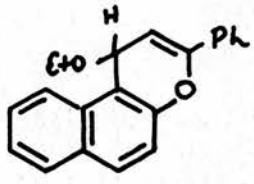
ii) the effect of the benzoyl group has been relayed

iii) evidence against the quinone theory of Royer and co-workers.

Following this the corresponding 2- hydroxy- 1- naphthylideneacetophenone (CII) was synthesised in a similar way and allowed to undergo the reaction. The synthesis was a little more complex than that of the preceding chalkone. First of all the condensation of 2- hydroxy- ∝ - naphthaldehyde and acetophenone was carried out by passing dry hydrochloric acid gas through an alcoholic solution of the aldehyde and ketone to give naphthaflavylium chloride (C).



C

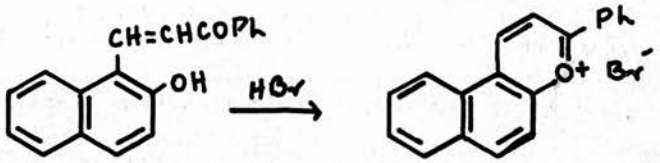


C1

The chloride was then heated with alcoholic sodium hydroxide to form 2- phenylnaphthapyranol- 4- ethyl ether (CI) which yielded the required vinyl ketone on boiling with alcohol (50%).

The Fission Reaction was carried out on this ketone with a reaction time of seven hours and impure starting material

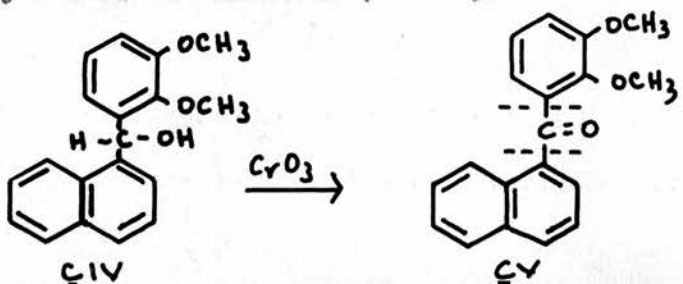
was recovered with no evidence of β - naphthol. A small quantity of orange-brown crystals were obtained which were insoluble in ether. Repeating the procedure for twenty-four hours gave only this orange-brown solid which was recrystallised from water containing a little hydrobromic acid. It was difficult to purify but analysed approximately for naphthaflavylium bromide (CIII). So the



CII CIII

vinyl ketone has undergone ring closure in preference to the fission reaction taking place. It is possible that steric factors play some part in this and the position of the side chain is such that it is more facile to form the oxonium bromide than to rupture the bond joining the side chain to the naphthalene nucleus.

Because of this increased activity and ease of fission in the naphthalene series the question arises as to whether a ketone such as 1- (2':3'- dimethoxybenzoyl)- naphthalene (CV), which has no hydroxyl or methoxyl in the naphthalene nucleus, would undergo fission. Again there are two possible positions for fission. The positions are indicated by the dotted lines in (CV).

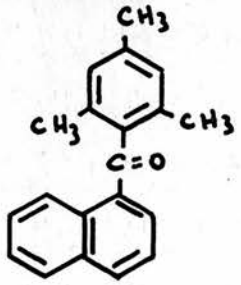


CIV CV

This ketone was prepared by a Grignard Reaction between α - naphthylmagnesium bromide and 2:3- dimethoxybenzaldehyde which gave the corresponding secondary alcohol (CIV). This was oxidised to the required ketone. The oxidation was carried out with chromic oxide after several attempts at an Oppenauer oxidation with aluminium isopropoxide and t- butoxide, with various hydrogen acceptors, had been tried. A little ketone was obtained during an oxidation with the latter catalyst (t- butoxide), and benzil as the acceptor but the yields were only approximately half those obtained with chromic oxide which were small (21%).

A seven hour treatment of the ketone produced demethylated material only with no evidence of fission. So the presence of a phenolic grouping in the naphthalene nucleus seems to be necessary before cleavage can take place.

In the benzene series it was proved that no fission took place with benzoylmesitylene (p. 58). This was further substantiated by the synthesis of naphthoylmesitylene or 1-(2':4':6'- trimethylbenzoyl)- naphthalene (CVI) by a Friedel-Crafts Reaction between α- naphthoic acid chloride and mesitylene.



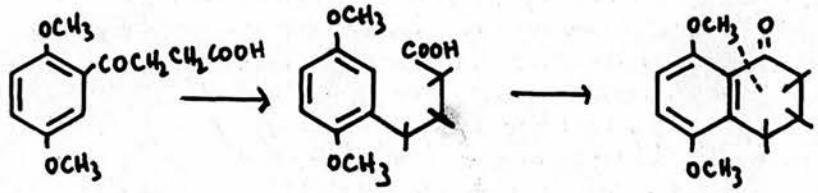
CVI

The ketone would not give a dinitrophenylhydrazone by Allen or Brady's method suggesting that the methyl groups are bulky enough to shield the carbonyl from attack. So they

must necessarily shield the α - carbon atom in the benzene nucleus from attack by protons. The bond between the carbonyl grouping and the naphthalene nucleus might therefore be more easily ruptured. However seven and twenty-four hour refluxes with the acid reagent gave 80 - 84% recoveries of the ketone with the complete absence of any acidic material. This shows definitely that, considering the ketone as a benzene derivative, the presence of a hydroxyl grouping is a necessity in the benzene nucleus before fission can take place. It was thought that benzoylmesitylene would have a sufficiently low activation energy associated with the appropriate bond to allow decomposition and certainly the increased resonance and conjugation due to the naphthalene ring ought to have reduced the activation energy low enough to allow fission.

It has been noted earlier (p. 22) that Hill and Short reported the existence of a ring fission reaction of a cyclic ketone when treated with this reagent mixture. The ketone they investigated was in the phenanthrene series. It was thought that a ketone such as a substituted tetralone might also undergo the fission reaction. Therefore 5:8-dimethoxy- α - tetralone (CIX) was synthesised. The first step in the synthesis was the formation of 2:5-dimethoxybenzoylpropionic acid (CVII) from an aluminium chloride catalysed reaction between hydroquinone-dimethyl- ether and succinic anhydride. This was reduced to the corresponding butyric acid (CVIII) by the Clemmensen method and the acid ring closed to the required ketone in

almost 70% yield using polyphosphoric acid. The ketone was purified chromatographically.



CVII CVIII CIX

p.133

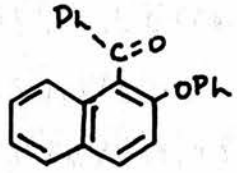
This cyclic ketone has the two methoxyl groupings in the aromatic nucleus and one is ortho to the ketonic grouping so it would seem to have a fair chance of fission, at the position indicated by the dotted line in (CIX), to give the 2:5- dimethoxybutyric acid (CVIII) or its demethylated counterpart. After twenty-four hours however only demethylated phenolic material was recovered. This gave a dinitrophenylhydrazone and so seemed to be the dihydroxyketone. Analysis showed that this was so. It would seem now that 6:8- dimethoxy- α - tetralone would have a better chance of cleavage for the methoxyls are ortho and para to the cyclic carbonyl grouping. It has been shown that 6-methoxy- α - tetralone does not give any fission product however (p.22).

To establish finally whether the presence of a hydroxyl grouping is necessary before cleavage of the ketonic residue can take place it was decided to synthesise a ketone with a stable ether grouping. It is well known that phenyl ethers are much more stable than the corresponding

methyl ethers and therefore a ketone such as 1- benzoyl-β - naphthyl phenyl ether (CX) may have a sufficiently stable ether grouping to withstand the de-alkylation reaction of the hydrobromic acid - glacial acetic mixture.

The ketone was synthesised by a Friedel-Crafts reaction between benzoyl chloride and β - naphthyl phenyl ether. A neutral red oil was produced from the reaction and it was purified chromatographically to give a pale yellow oil. This however, would not give a dinitrophenylhydrazone by the usual methods. The analysis of the oil was low in carbon content (1%) suggesting it was not quite pure. An attempt to purify it further by distillation resulted in a decomposition of the ketone to β - naphthyl phenyl ether (identified by analysis). After standing several weeks in a refrigerator the oil showed signs of crystallising.

The oil was allowed to undergo the fission treatment for varying times. After three hours a trace of benzoic acid was identified along with a small amount of a phenolic solid which melted in the region 70 - 80° and was probably impure β - naphthol. The neutral fraction from the reaction was a reddish oil which crystallised after chromatographic purification and which analysed fairly well for the starting ketone. A recovery of 70 - 80% of this solid was obtained. Therefore it would seem that the starting ketone is in fact a solid.



CX

Attempts at the cleavage of the ketone (CX) were repeated with reaction times of five and twenty-four hours. In each case however only the same colourless solid was recovered in good yield with a trace of benzoic acid and β - naphthol (the phenolic material was steam distilled to give a fairly pure specimen of β - naphthol).

The reaction was repeated using phosphoric acid in a solution of glacial acetic. Here again the colourless solid was the main product with traces of the acid and phenol.

From this series of reactions it appears that fission is almost non-existent. The traces of benzoic acid obtained are presumably due to a slight decomposition of the phenyl ether shown by the presence of a little β - naphthol. The fact that only traces of decomposition products are obtained even after twenty-four hours shows that fission is very difficult even under these prolonged conditions. When these results are compared to the ease with which the corresponding methyl ether decomposes (80% in seven hours) then the obvious conclusion is that the presence of a hydroxyl is a necessity for fission but whether its effect is purely electromeric or to allow a tautomeric formation of a quinonoid type of molecule, as described by Royer, to take place, is not quite clear.

Phosphoric acid is a stronger reagent than HBr and so treatment of the ketone with it ought to introduce a better chance of fission. On the other hand phosphoric has been shown to be much less effective as a de-alkylation reagent (p. 77) so it is interesting to see what happens when it is used.

The use of other reagents: Several other reagents were used to bring about the decomposition of 1- benzoyl- 2- methoxynaphthalene. As mentioned above phosphoric acid is a possible reagent. Rosenmund and Schnurr[11] used it and demonstrated that it could bring about the Reversal of the Fries Reaction. Klages[15] and other workers employed it to accomplish the fission of many alkyl substituted ketones showing it was a powerful reagent. In this work it was used in glacial acetic but first of all β - naphthyl methyl ether was treated with mixtures containing varying concentrations of phosphoric acid until no demethylation of the ether occurred. This concentration (1 part acid to 4 parts acetic) was then used in the treatment of the ketone but demethylation and fission both took place with the production of benzoic acid (74%) and β - naphthol (55%). The neutral fraction yielded β - naphthyl methyl ether (20%). With a concentration of 1 part phosphoric to 8 parts acetic no demethylation occurred and β - naphthyl methyl ether was produced in 60% yield. Fission has not been so complete in this latter case and this cleavage has evidently taken place by a straightforward hydrolysis of the ketonic grouping as no rearrangement is possible in the absence of a hydroxyl group. The fact that the yield of fission products is slightly higher in the case where demethylation did occur to some extent may be explained by the presence of both the straightforward hydrolytic fission and by the fact that the existence of the hydroxyl, as a result of demethylation, will

give a slightly stronger electromeric effect at the α - carbon than that produced by the methoxyl grouping. The fact that β - naphthyl methyl ether is a product of the fission seems to rule out the possibility of the fission taking place by a Reverse Fries mechanism.

With sulphuric acid, which is another vigorous reagent, a thirty minute treatment of the ketone resulted in the formation of benzoic acid (44%) and the methyl ether (46%). Again sulphuric will not demethylate readily and so the reaction is one of hydrolytic fission. This work also indicates that the fission with hydrobromic acid is also a straightforward fission and not a Reverse Fries Reaction or fission via intermediate quinonoid formation.

In order to establish the effect of increasing acidity on the rate of the reaction it was decided to carry out standard reactions on the same ketone using acetic and the stronger dichloracetic acid as solvent for the hydrobromic acid treatment. After one hour with the latter as solvent the yield of fission products was much higher than similar treatment using acetic acid in the reaction. The reaction temperature was kept the same in both cases as evidently a difference in reflux temperature is going to affect the rate of the reaction considerably. This was only some preliminary large scale work on the effect of acidity on the reaction rate and the problem is dealt with in detail in the quantitative section.

In a general comparison with the ketones investigated in the benzene series it is evident that fission is much

easier in the naphthalene series. This of course is to be expected because of the increased double bond character of some of the bonds in the naphthalene nucleus. So one hydroxyl grouping is found to be enough to increase the electron density sufficiently at the reactive centre to allow the cleavage of an ortho or para substituted ketone. Benzene, in contrast, requires three such groupings (or two in the positions ortho to the ketonic group) before the fission reaction becomes evident.

Sufficient indication has been given to favour the idea of the direct attack of a proton at an electronegative centre as the mechanism of the fission reaction. Certainly there is no evidence for the existence of a Reverse Fries reaction and although in some cases there is the possibility of quinonoid formation the evidence is definitely in favour of a proton attack.

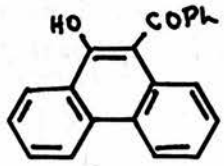
SECTION IV

Phenanthrene Series.

In this section several ketones, with a still larger aromatic nucleus, were synthesised and allowed to undergo the reaction.

The 9,10- bond in phenanthrene is almost ethylinic in character. It is, for example, attacked by osmium tetroxide and other double bond reagents. From the energy point of view the so called bond localisation energy of this bond is 16 k.cals/mole compared with 30 k.cals/mole in benzene and 22 k.cals/mole for the 1,2- bond in naphthalene. So this gives a strong indication of the enhanced reactivity and double bond character of this linkage.

Therefore a ketone such as 9- hydroxy- 10- benzoylphenanthrene (CXI) should undergo fission very readily. The ketone was synthesised from the benzoyl derivative of 9- hydroxyphenanthrene with aluminium bromide as catalyst and nitrobenzene as the inert solvent. It was found that a yield of 75% of 9- hydroxyphenanthrene was produced after a two hours treatment of the ketone with the reagent mixture.



CXI

Since the fission had been achieved so readily it was decided to try a reaction at room temperature. The ketone was dissolved in the reaction mixture, cooled to room temperature and left for forty-eight hours. Unfortunately a large amount of the ketone crystallised out on standing. The solid was filtered off and the solution diluted. This yielded a trace of benzoic acid and some impure starting ketone which gave a melting point depression when admixed with starting material. The presence of 9- hydroxyphenanthrene may have been responsible for this depression.

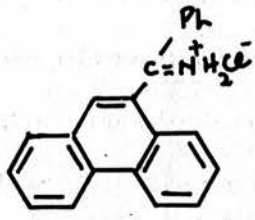
The corresponding methyl ketone, 9- hydroxy- 10- acetylphenanthrene also gave a 75% yield of the phenol after two hours under reflux. The methyl ketone was more soluble in the reaction medium and when allowed to stand at room temperature for twenty-four hours no solid settled out. Dilution of the reaction mixture gave an 88% yield of 9- phenanthrol.

So the ethylinic nature of the double bond at the 9,10 positions has permitted an ease of fission not found with any ketone investigated so far. It seemed that the unsubstituted ketone 9- benzoylphenanthrene (CXIII) might undergo fission readily.

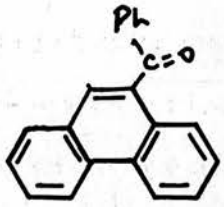
p.147

Three methods of synthesis of this ketone were tried. The first was by interaction of 9- phenanthryl magnesium bromide and cyanobenzene. On carrying out this according to the method reported by Bachmann[64] it was found that a white complex always settled out and the product was a

yellow solid which would not form the ketimide hydrochloride (CXII).

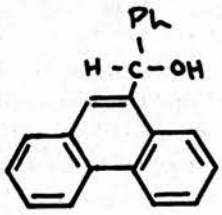


CXII



CXIII

So the Grignard reaction was tried between benzaldehyde and 9- phenanthrylmagnesium bromide. A pale yellow oil which analysed quite well for the carbinol (CXIV) was produced but this oil could not be oxidised to the ketone. Chromic oxide and sodium dichromate produced phenanthraquinone. The Oppenauer oxidation with aluminium isopropoxide catalyst and acetone or cyclohexanone as hydrogen acceptors had no effect. So this method was abandoned.



CXIV

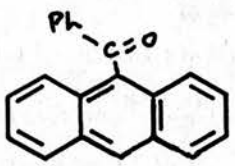
Attempts to obtain the ketone by a Grignard reaction between 9- cyanophenanthrene and phenylmagnesium bromide also failed. The white complex formation, mentioned above, was noticed again. Finally the original Grignard with 9- phenanthrylmagnesium bromide was repeated in dry benzene as

solvent. No complex appeared during the reaction and a colourless viscous oil was produced on decomposition of the hydrochloride (CXII). This was purified chromatographically and it crystallised on standing as colourless prisms. The melting point however (79 - 80°), was lower than that given by Bachmann (loc. cit.) for 9- benzoylphenanthrene. However the solid analysed perfectly for the required ketone.

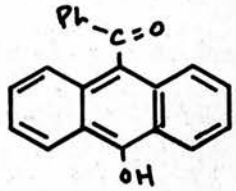
Treatment of the product with hydrobromic acid in glacial acetic for seven and twenty-four hours gave only the starting ketone in quantitative yield. No evidence of benzoic acid was found.

Following this it was decided to see how 9-benzoylanthracene (CXV) would react under similar conditions. Cook[21] has shown that this ketone may be cleaved using sulphuric acid in acetic. After two and seven hour treatments of the ketone no fission products were obtained. However after twenty-four hours a 77% yield of benzoic acid was produced. An impure neutral fraction was separated by chromatography to give 72% anthracene and 12% of the original ketone. Therefore it requires longer treatment before fission can take place. The well known electrophilic attack at the 9 and 10 positions in the anthracene molecule indicates that these positions in the molecule will have a fairly high electron density associated with them. However it is not so large as that produced by an adjacent hydroxyl grouping but the fact that fission does take place shows it is considerable. The relative ease of decomposition of 9-benzoyl- 10- hydroxyanthracene (CXVI) shows the effect of the

presence of the phenolic group in the conjugated position (Cook, loc. cit.).

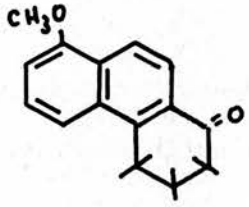


CXV

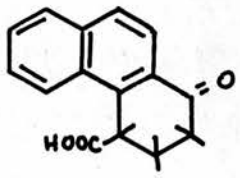


CXVI

It has been mentioned earlier that Hill and Short[42] obtained fission of a cyclic methoxy ketone, 1- oxo- 8- methoxy- 1:2:3:4- tetrahydrophenanthrene (CXVII). The relationship between the position of the methoxyl grouping and the bond which is ruptured from the aromatic naphthalene nucleus is not evident. A similar unsubstituted ketone 1- oxo- 4- carboxy- 1:2:3:4- tetrahydrophenanthrene (CXVIII) was treated under reflux for twenty-four hours but no ring opening was achieved and about 85 - 90% recovery of the ketone was obtained.



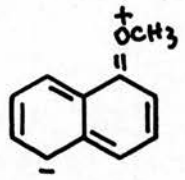
CXVII



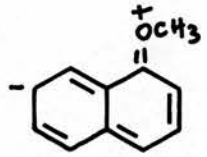
CXVIII

The fact that there is a carboxyl grouping in this molecule should make no difference as it is in the saturated ring and so no electromeric effect can take place due to its presence. The fact that this latter ketone gave no fission shows that the methoxyl in the 8- position is essential for

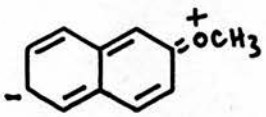
fission to occur. Normally in the naphthalene nucleus there is a conjugative effect between the 1,5- (CXIX a) or 1,7- positions (CXIX b) but none between the 1,6- positions.



CXIXa.

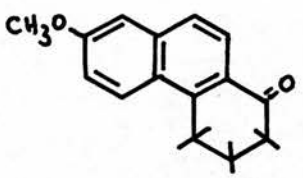


CXIXb.



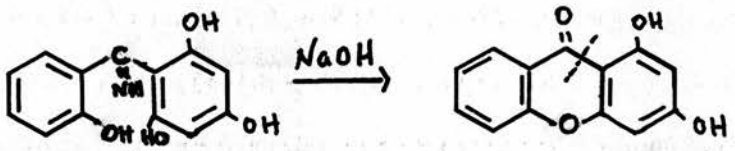
CXX

On the other hand the 2,6- positions show the conjugative effect (CXX). So the cyclic ketone 1- oxo- 7- methoxy- 1:2:3:4- tetrahydrophenanthrene (CXXI) might be expected to show the ring fission phenomenon but curiously enough this compound has been shown to undergo demethylation only (43).



CXXI

Still in this field of cyclic ketones, 1:3- dihydroxyxanthone (CXXIII) was synthesised to see if it would cleave as shown by the dotted lines. The synthesis was carried out by condensing salicyl nitrile with phloroglucinol in the presence of dry hydrochloric acid gas to produce the ketimine (CXXII). Treatment of this with sodium hydroxide split out ammonia and gave ring closure to the required product at the same time.



CXXII CXXIII

Seven and twenty-four hour treatments of the cyclic ketone resulted only in the recovery of the xanthone. This cyclic ketone is analogous to benzoylphloroglucinol which underwent fission readily enough. The xanthone has hydroxyl groupings ortho and para to the carbonyl group and so fission would be expected at the point indicated in (CXXIII). The effect of ring closure has been to reduce the electron density build up at the required point of fission, the reduction being sufficient to withstand the attack of a proton at this point.

SUMMARY.

This experimental work has given several interesting examples of ketonic fission and the increase in ease of fission with increase in aromaticity of the nucleus of the rearranging ketone has been demonstrated.

DISCUSSION

SECTION V

Quantitative Section.

The discussion of this section of the work will be fairly short because it will be covered in detail in the experimental section (p. 153).

The large scale work with acetic and dichloracetic acid, described in the naphthalene series (p. 77), indicated that the rate of the fission reaction with 1-benzoyl- 2- hydroxynaphthalene was increased by increasing the acidity of the reaction medium. The quantitative work has proved this beyond doubt.

The fission of the ketone was investigated by using a spectrophotometric method to follow the change in its concentration as the reaction proceeded. The original idea of using acetic and dichloracetic to give different acidities had to be abandoned because of the formation of a deeply coloured solution when dichloracetic was used. This colour upset all the spectrophotometric readings. Instead the glacial acetic - hydrobromic acid mixture was diluted with water to change the acidity and a definite decrease in rate was observed with decreasing acidity. In fact a rough proportionality was noticed between the rate decrease and the acidity change.

The graph of change in concentration of the ketone against time gave an exponential type curve and the plot of the logarithm of the change in concentration against time produced a straight line graph. This indicated first order kinetics. The rate constants for the reaction were calculated using the First Order Equation:

$$k = \frac{2.303}{t} \cdot \log_{10} \frac{a}{(a - x)}$$

with the usual nomenclature. The results fitted this equation very well. So the reaction is first order with respect to the ketone.

The fact that the rate is affected by the acidity in a roughly proportional way means that the rate of the reaction will be given by the equation:- Rate = $k [H^+] [\text{ketone}]$. The reaction is then pseudo-unimolecular, the pseudo-unimolecularity arising because of the excess of hydrogen ions present in the reaction medium.

In the great amount of work performed in the field of thermal decarboxylation of aromatic acids evidence for a bimolecular mechanism of decarboxylation has been reported. Schenkel and Schenkel-Rudin[65] in 1949 indicated that some of these acids are decarboxylated by a bimolecular electrophilic substitution mechanism (designated S_E2):-

$$H^+ + R\,COOH \rightarrow HR + CO_2 + H^+$$

In this reaction the rate is determined by the attraction of a proton by the acid.

Anthracene 9- carboxylic acid has been shown to lose

carbon dioxide by the S_E2 mechanism. Further it was pointed out that the α - carbon atom in this acid has a high electron density and so favours the approach of a proton.

Schubert[66] has shown that mesitoic acid (2:4:6-trimethybenzoic) shows a proportionality between the pseudo first order constants and the concentration of the hydroxonium ion. So the reaction will take place by the S_E2 mechanism. This work of Schubert gives a quantitative demonstration of the dependence of the rate of loss of carbon dioxide on the acidity and so gives a very good proof for the existence of the S_E2 mechanism.

Brown and others[57] carried out an investigation into the kinetics of decarboxylation of a series of hydroxybenzoic acids and they found that these acids with a high electron density at the α - carbon atom are decarboxylated by an S_E2 mechanism. The rates of reaction increased with the increasing number of ortho and para hydroxyl groupings. This is the order in which the acids will facilitate the attack of a proton.

By analogy with this work on decarboxylation it is evident the mechanism of the ketonic fission reaction is of the S_E2 type, i.e., a bimolecular electrophilic substitution reaction. The qualitative work has proved the effect of increasing the electron density at the α - carbon atom thus facilitating the approach of a proton and the quantitative work has shown a dependence of the rate of the reaction on the acidity. The combination of both sets of results provides sufficient evidence for saying that the reaction is of the SE2 type.

FINAL SUMMARY

From this research several points are apparent:

(i) The presence of a hydroxyl grouping in an ortho or para position is necessary.

(ii) The ease of fission of these aromatic ketones is enhanced by the presence of further hydroxyl groups and also by methyl groupings in the nucleus.

(iii) The ketonic residue also plays some part, since hydroxy benzyl compounds do not undergo fission.

(iv) Evidence is given to show that the initial reaction is attacked by a proton at the negative centre resulting from electromeric or inductive effects.

(v) The fission is certainly not a Reverse Fries Reaction and intermediate quinonoid formation is insufficient to account for all the fissions observed.

(vi) The ease of fission is dependent on the double bond character of the bond (or bonds) separating the hydroxyl and ketonic groupings.

(vii) Change of acidity of the reaction medium has the expected effect of altering the rate of the reaction which has been shown to be a bimolecular electrophilic substitution reaction.

EXPERIMENTAL INTRODUCTION

(i) Unless otherwise stated all yields are reported as the percentage of the theoretical yield.

(ii) All melting points were determined by the use of a Kofler micro melting point apparatus.

(iii) Fluorescence observations were carried out with the use of a Hanovia lamp.

(iv) Chromatographic work was performed with B.D.H. standard alumina.

(v) Analyses were carried out by Doctors Weiler and Straus, Oxford.

EXPERIMENTAL

SECTION I

Benzene Series

1. o- Hydroxybenzophenone.

After an unsuccessful attempt to prepare this ketone according to the method of Graebe and Ullman, (Ber., 1896, 29, 824) which yielded a non-crystallisable syrup it was prepared by a Reverse Friedel-Crafts reaction (Johnson and Glen, J.A.C.S., 1949, 71, 1092) from salicylic acid chloride keeping the temperature below 60°. Pale yellow crystals m.p. 36 - 38° (Lit., 39°) were obtained by crystallisation from methanol. Yield - 50%.

2:4- Dinitrophenylhydrazone- orange red crystals from glacial acetic acid m.p. 246 - 248°.

Hydrobromic Acid Treatment:-

The ketone (2.0g.) was dissolved in glacial acetic (40 ccs.) and hydrobromic acid (40 ccs.) added. The resulting yellow solution was boiled for 7 hours, most of the acetic acid then removed by distillation and the residue poured into water (100 ccs.). This solution was extracted with ether (3 x 25 ccs.) and the ether solution in turn extracted with

(i) Sodium carbonate - on acidification this yielded no benzoic acid

(ii) Sodium hydroxide - on acidification and subsequent

extraction with ether a brown oil was obtained which, on seeding with some of the starting ketone, immediately gave a lemon yellow solid (1.60 g.) - fern shaped crystals from methanol m.p. 34 - 37°. This solid was steam distilled in case any phenol was present. However only the o- hydroxybenzophenone was obtained m.p. 37 - 38°. Mixed m.p. 36 - 8° (with starting ketone). The crude material from the reaction gave a red brown colour with ferric chloride in alcohol which corresponded with the colour found on testing the starting material. (Phenol gives a green colour in alcohol.)

Recovery of starting ketone - 80%.

---

2. p- Hydroxybenzophenone.

The recrystallised ketone (L. Light & Co.) m.p. 134 - 135° (4.0 g.) was boiled with glacial acetic (60 cc.) and hydrobromic acid (60 cc.) for seven hours.

Again no benzoic acid was found in the carbonate extract. Phenolic material (3.6 g.) was recovered as a brown sticky solid which, on recrystallisation from aqueous methanol, had m.p. 130 - 132°. M.m.p. - no depression.

Recovery of starting material - 90%.

---

3. 2:4- Dihydroxybenzophenone (Benzoylresorcinol).

Reference: Hoesch, (Ber., 1915, 48, 1130.)

Resorcinol (10.0 g.) was treated with cyanobenzene (10.0 g.) in pure dry ether (60 ccs.) in the presence of

zinc chloride (4.0 g.) with a stream of dry hydrochloric acid gas passing through the solution. After standing overnight an oily lower layer was visible. This was separated, dissolved in 5N. hydrochloric acid and the solution extracted twice with ether to remove any organic material not in the form of the ketimide - hydrochloride. The acid layer was boiled for twenty minutes and extracted twice with ether (2 x 40 ccs.). This yielded a brownish oil which gave white needles from boiling water (0.40 g.) m.p. 141 - 142°. Lit. 144°.

NOTE: Hoesch reported yields of 40% for this reaction. However repetition of the above preparation gave the same small yield of ketone. On shortening the duration of the experiment to three hours (Hoesch's time) no lower layer separated.

Hydrobromic Acid Treatment:-

The ketone (0.30 g.) was boiled in glacial acetic (15 ccs.) and hydrobromic acid (15 ccs.) for seven hours.

No benzoic acid could be found in the carbonate extract but the hydroxide extraction, on acidification, yielded a copious white precipitate which was filtered and dried (0.28 g.) m.p. 139 - 140°. M.m.p. - no depression.

Recovery of original ketone - 83%.

---

4. 2:4:6- Trihydroxybenzophenone- Benzoylphloroglucinol.

Reference: Hoesch, (loc. cit.)

This was carried out in the same way as the benzoylresor-

cinol preparation above, but again the reaction time had to be extended from a three hour passage of dry hydrochloric acid gas to one of five hours duration before the oily lower layer settled out. Special care was taken to ensure that the zinc chloride used was dry by fusing it, before its addition to the reaction mixture.

After extracting unreacted organic material from the oil with ether as usual, the oil was dissolved in dilute sulphuric acid (50 ccs.) to form a ketimide-sulphate which solidified on cooling. It was decomposed by boiling for thirty minutes and the resulting oil was repeatedly extracted with benzene to give a yellow crystalline solid. Some of the oil, however, could not be extracted but when xylene or chlorobenzene were used a further crop of crystals were obtained. This is the hydrate which was distilled with dry benzene to remove the water of crystallisation. The yellow elongated prisms obtained melted at 165-166°. Lit. - 165°.

Yield - 3.85 g. (35%) from 6.0 g. phloroglucinol.

Again this yield is much lower than that reported by Hoesch (65%).

Hydrobromic Acid Treatment of the Ketone:

It was found that this phenolic ketone after a seven hour reflux gave benzoic acid and phloroglucinol. However the solubility of the phloroglucinol is such that with the volumes of aqueous solutions obtained on dilution of the reaction mixture most of the phenol remained in the aqueous layer and could not be extracted readily with ether. So a method which would give reasonably accurate estimations of

the phloroglucinol present was required. The difficulty was to find a reagent which was specific for phloroglucinol, i.e., which would not react with any unreacted ketone which might have been present.

Phloroglucinol is used in sugar chemistry to estimate pentoses which are first degraded to furfural which then gives a complex with the phenol (Chem. & Ind., 1916, 35, 731). So conversely it was thought that furfural might be used to estimate the phloroglucinol.

Several "blank" reactions with furfural and benzoyl-phloroglucinol showed that no complex was formed using varying concentrations of the ketone. Furfural gives no precipitate with benzoic acid, the other product of the reaction and so there were no complications in its use. Again the question of the acidity of the solution from the reaction was shown (from control experiments) not to be critical. (Furfural estimations are normally done in 12% hydrochloric acid.) The acidity of the solutions used here were about 20% with respect to hydrobromic acid after removal of most of the acetic and dilution with water.

Estimation of Phloroglucinol formed by a seven hour reflux:

The ketone (1.0 g.) was boiled in glacial acetic (35 ccs.) and hydrobromic acid (35 ccs.). A red solution was formed. As usual the acetic acid was nearly all removed, the solution diluted with an equal volume of water and excess furfural added (circa 5 - 10 ccs.). (The dilution has to be such that the concentration of phloroglucinol present does not fall below 0.015 g./100 ccs. or precipitation is incomplete.)

The solution was then set aside for twenty-four hours and the resulting precipitate filtered off using a sinter glass crucible. After washing free from acid it was dried at 100 - 105° to constant weight.

Control Experiments:

Several control experiments were then carried out with known weights of phloroglucinol (0.10 g.) dissolved in 20 - 25% hydrobromic acid and the weights of the complex found. The average of a number of these "blank" determinations was taken and this was used to calculate the weight of phenol produced by the ketonic fission. It was found that 0.100 g. phloroglucinol gave 0.210 g. of complex. The error involved in this method of determination was found to be ± 4%.

From the seven hour reflux a yield of 40% phloroglucinol was calculated. Values of 36% and 39% were obtained from two other similar determinations using 0.24 g. and 0.50 g. of the ketone respectively.

Estimation of Benzoic Acid from a seven hour Reflux.

The reaction was carried out as above using (1.0 g.) ketone and the diluted reaction solution was extracted with ether (3 x 30 ccs.). This ether solution on extraction with carbonate (3 x 15 ccs.) gave a reddish carbonate solution which, on acidification and extraction with ether, yielded 0.19 g. benzoic acid m.p. 119 - 121°. M.m.p. 118-121°.

% Yield - 36.

Further experiments using 0.36 g. and 0.55 g. ketone gave 27% and 33% acid respectively.

SUMMARY:

PHENOL		ACID	
Wt. of Ketone (gms.)	% Phloroglucinol	Wt. of Ketone (gms.)	% Benzoic Acid
1.00	40	1.00	36
0.50	39	0.55	33
0.24	36	0.36	27

Estimation of Products from Sixteen Hours Treatment::

It was decided to extend the above results by increasing the reaction time to see if there was a consequent increase in the fission reaction. On increasing the reaction time to sixteen hours however, a complication arose in the formation of a complex between the phenol formed and the hydrobromic acid. This complex settled out during the reaction as orange-red crystals after refluxing for 11 - 12 hours. Some of these crystals were filtered off and found to decompose about 250° changing in colour, through orange to black, about 200°. They were insoluble in non-polar solvents like benzene and petrol ether and soluble in water, alcohol and glacial acetic (slightly). No evidence for the formation of this complex was found in the seven hour reaction. This compound has been shown to be of the type HBr.2M, a clathrate type compound, where M is the phenol molecule. (Gomberg and Cone, Ann., 1910, 376, 237, and Powell, J.C.S., 1948, 71.)

Several "blank" determinations were carried out on this

compound with furfural, as before, and it was found to give a sufficiently accurate formation of the furfural complex to merit its use in determining the quantity of phenol formed during the sixteen hour reflux.

A series of experiments were carried out in the normal way and the weights of phloroglucinol formed were calculated from the standard or "blank" average. The benzoic acid produced was estimated, in separate reactions, by direct weighing as before.

SUMMARY:

PHENOL		ACID	
Wt. of Ketone (g.)	% Phloroglucinol	Wt. of Ketone (g.)	% Benzoic Acid
2.45	81	2.00	45
1.05	72	1.25	44
0.36	70	0.35	37

The percentage of phenol produced has risen to about double that of the previous results. This was as expected. The benzoic acid however has not shown a similar increase, probably due to the method of estimation which will be much less accurate than that of the furfural method.

---

5. 2:3:4- Trihydroxyacetophenone.

This ketone (2.0 g.) was treated for seven and sixteen hours. The alkali extract of the original ether extract of the reaction mixture gave a reddish solid on acidification. It was in turn extracted into ether, dried and the ether removed to give colourless needles from water

after treatment with charcoal. Yield - 1.76 g.
m.p. 172 - 173° with sublimation above 130°.
Mixed m.p. with starting ketone - no depression.
Recovery - 88%.

---

6. 2:6- Dihydroxyacetophenone.

This was prepared by the method described by Baker (J.C.S., 1934, 1953). 7- Hydroxy- 4- methylcoumarin (Org., Syntheses, 21, 23) was prepared from resorcinol (74 g.) and acetoacetic ester (86 g.) to give 92 g. (77%) crude coumarin which was acetylated with acetic anhydride (74% yield). The powdered crude acetyl derivative was used directly in the Fries reaction.

The acetate (16 g.) was treated with aluminium chloride (36 g.) and the mixture heated rapidly to 125° when the mixture was shaken vigorously for 5 minutes. Finally heating was continued at 170° for 2 hours, and the mixture decomposed with ice and hydrochloric acid and by heating on the steam bath for 30 minutes, to complete the decomposition. The greyish-black solid obtained was treated in a Soxhlet extractor for 2 hours with (100 - 120°) petrol ether and the 4- methyl- 6- hydroxy- 8- acetylcoumarin was extracted in a very pure state.

Yield - 8.2 g. (51%).

This compound (8.0 g.) was heated on the steam bath with sodium hydroxide in an atmosphere of nitrogen for 5 hours. The yellow solid obtained by acidification was charcoalled in alcohol and finally crystallised from water as sandy-

yellow crystals m.p. 151 - 153°. Lit. - 153°.

Yield - 3.50 g. (65%).

Hydrobromic Acid Treatment:-

2:6- Dihydroxyacetophenone (1.0g.) with glacial acetic (20 ccs.) and hydrobromic acid (20 ccs.) gave a brownish-red solution which was refluxed for seven hours; the reaction mixture diluted with water (100 ccs.) and extracted with ether. The ether solution was well washed with water and dried (sodium sulphate), to give a mobile oil which would not crystallise. It was extracted with boiling petrol ether (100 - 120°) to give colourless crystals (recrystallised from xylene) m.p. 104 - 106°. Mixed m.p. with resorcinol 105 - 108°.

Yield - 75%.

This was repeated with 3.0 g. ketone in a three hour reflux. Again an oil (2.0 g.) was obtained which gave resorcinol (1.80g.) which was identified by m.p. and m.m.p. and the dibenzoyl derivative m.p. 116 - 117°. Lit. - 117°.

Yield - 82%.

Attempted Preparation of 2:6- Dihydroxybenzophenone:

The same method used for the methyl ketone above was tried. However no 4- methyl- 7- hydroxy- 8- benzoylcoumarin was obtained from the Fries reaction. This rearrangement was tried (i) without solvent as above at 170°, (ii) using carbon disulphide and (iii) nitrobenzene

at 50°, 100° and 200° with a reaction time of two hours. No ketone was obtained.

It was also tried with the method described by Bruce et al., (J.C.S., 1953, 2403) using a fused melt of aluminium chloride and sodium chloride at 180° - 200° but again no ketonic material could be isolated.

7. 2:4:6- Trihydroxychalkone.

Phloroglucinol aldehyde (4.0 g.) (prepared from a Hoesch condensation with zinc cyanide and dry hydrochloric acid gas) and acetophenone (4.0 g.) were added to a solution of potassium hydroxide (10 g.) in 40ccs., alcohol (50%). The mixture, after heating at 95 - 100° for two hours yielded a red crystalline solid which was recrystallised from water m.p. 216 - 218°.

Yield - 2.40 g. (36%).

2:4- Dinitrophenylhydrazone - m.p. 239 - 241°.

Hydrobromic Acid Treatment:-

The chalkone (1.0g.) after hydrobromic acid treatment for seven hours gave a brownish solid (0.80 g.) which settled out during the reflux. The reaction gave no acidic material (sodium carbonate) suggesting no ketonic fission. The brown solid obtained was very soluble in water. It was dissolved in glacial acetic (charcoal), to which some hydrobromic acid (10%) had been added, and the solution filtered through a sintered glass filter. Brown needles were obtained on cooling which darkened

gradually on heating to 300 - 320° but no melting was observed.

This proved to be a hydrobromic acid complex. (Cf. treatment of benzoylphloroglucinol.) It is noteworthy that this complex was formed during a seven hour treatment whereas with benzoylphloroglucinol the complex only formed after treatment of the ketone for sixteen hours.

Analysis of complex: Found: Br - 22.7%.

Required for $C_{15}H_{13}O_4.HBr$ - 23.9%.

The exact nature of the complex was not investigated but from the analysis it is empirically one molecule HBr and one of the ketone and so it differs from the phloroglucinol complex which Gomberg and Cone showed by analysis to be two molecules of the phenol to one of hydrobromic acid.

---

8. 2- Hydroxy- 4- methylbenzophenone and 2- Methyl- 4- hydroxybenzophenone.

The benzoyl derivative of m- cresol (20 g.) (prepared from the phenol with benzoyl chloride in pyridine) was treated with aluminium chloride (24 g.) for one hour at 130 - 140° on an oil bath. The addition of the aluminium chloride was made in small portions over 15 minutes, with cooling, because of the brisk initial reaction. The mixture formed a brown oily complex which was decomposed, after cooling, by pouring on to a mixture of ice and dilute hydrochloric acid. On standing, this gave a brown oil which was taken up in ether, washed well with water and

dried over sodium sulphate. The resulting oil was triturated with methanol to give a yellow solid (3.70 g.). This was recrystallised from benzene - petrol ether (60 - 80°) - lemon yellow stout prisms m.p. 53 - 55°. Lit. - 60° (Hamada, Science Reps., Tôhoku Imp., Univ., First Ser., 1933, 22, 55) for 2- hydroxy- 4- methylbenzophenone.

2:4- Dinitrophenylhydrazone - pale red needles from glacial acetic acid m.p. 235 - 237°.

Analysis: Found: N - 14.2%.

Required: N - 14.3%.

The methanol extracts from the above trituration gave a sticky solid which recrystallised from aqueous methanol as almost colourless elongated prisms (4.30 g.) - m.p. 135 - 136°. Lit. - 129° (loc. cit.) for 2- methyl- 4- hydroxybenzophenone

2:4- Dinitrophenylhydrazone - bright red needles from glacial acetic acid m.p. 234 - 235°.

Analysis: Found: C - 60.5;H - 4.1

Theory: C - 60.9;H - 4.4.

(for $C_{20}H_{16}O_5N_4$)

This method of separation of the isomers proved more satisfactory than steam distillation which was slow and yielded only a small amount of the 2- hydroxy- isomer in the distillate.

Hydrobromic Acid Treatment:-

a) 2- Hydroxy- 4- methylbenzophenone

The ketone (0.5 g.) was refluxed with glacial acetic

acid and hydrobromic acid. After seven hours one half of the yellow reaction mixture was removed and worked up as usual. No trace of benzoic acid was obtained but the sodium hydroxide extract yielded 0.22 g. starting material (88%).

The remainder of the solution was refluxed for twenty-four hours altogether. The carbonate extract of the original ether extract of the reaction mixture gave 0.02 g. benzoic acid (14%) (m.p. and m.m.p.). The phenolic portion yielded 0.15 g. (60%) starting material m.p. 52 - 55°. M.m.p. - no depression.

---

b) 2- Methyl- 4- hydroxybenzophenone

The ketone (2.0 g.) was treated as above. No benzoic acid was obtained after seven hours and a quantitative yield of starting ketone was recovered (94%).

After 24 hours very little darkening in colour of the original yellow solution had taken place; however, benzoic acid (0.13g.) (23%) was obtained. The sodium hydroxide extract gave a brown oil which was steam distilled. The distillate yielded a trace of colourless oil which gave a blue-violet colour with ferric chloride similar to that obtained on testing m- cresol.

The residue from the distillation crystallised on cooling the aqueous solution to give 0.5 g. starting material (50%) m.p. 128 - 131°. M.m.p. 130 - 132°.

---

9. 2- Hydroxy- 5- methylbenzophenone.

Reference: Chakravarti and Bera (J. Ind. Chem. Soc., 1944, 21, 109).

p- Cresyl benzoate (10 g.) treated with aluminium chloride (12 g.) and heated at 130 - 140° for 1 hour gave 7.50 g. ketone (75%) - lemon yellow plates from dilute alcohol m.p. 86 - 87°. Lit. 87°.

Hydrobromic Acid Treatment:-

The ketone (2.0 g.) gave a lemon yellow solution which was refluxed for twenty-four hours. After seven hours one half of the reaction mixture was separated off and, on allowing it to cool, a quantitative yield (95%) of the starting ketone was deposited - (m.p. and m.m.p.)

The twenty-four reaction gave no benzoic acid. The bright orange sodium hydroxide solution yielded a yellow solid (0.90 g.) on acidification which again was the starting ketone m.p. 84 - 86°. M.m.p. 83 - 85°.

Recovery - 90%.

---

10. 2- Methyl- 4- hydroxy- 5- isopropylbenzophenone (Benzoylthymol).

Reference: Orndorff and Lacey, J.A.C.S., 1927, 49, 818.

The ketone was prepared by the Friedel-Crafts Reaction. Thymol (5.0 g.) was dissolved in dry freshly distilled nitrobenzene (70 ccs.) and to the stirred solution aluminium chloride (4.8 g.) was slowly added. After solution was complete, benzoyl chloride (4.7 g.) in nitrobenzene (30 ccs.) was slowly dropped into the cooled

solution. Vigorous evolution of hydrochloric acid followed and after two hours the solution was heated to 60° for one hour with constant stirring. The reaction mixture was decomposed as usual and the solvent (with any unreacted thymol) removed by steam distillation to leave a brown oil which was extracted with ether. The yellowish green sodium hydroxide extract yielded an almost colourless solid which, after treatment with charcoal and crystallisation from alcohol, gave colourless crystals (3.50 g.) m.p. 149 - 150°. Lit. 150°.

Hydrobromic Acid Treatment:-

The ketone (1.0 g.) on refluxing for seven hours gave benzoic acid (0.1 g.) (22%) - m.p. and m.m.p. The phenolic extract yielded white crystals (0.4 g.) of starting material m.p. 154 - 155.5°. M.m.p. - no depression. Recovery - 40%.

The original ether extract of the diluted reaction mixture gave 0.18 g. starting ketone (total recovery 58%) along with a trace of oily material which may have been thymol but which could not be identified.

---

11. 2- Hydroxy- 4:6- dimethylbenzophenone.

Reference: Baddeley, J.C.S., 1943, 274.

The benzoyl derivative of 3:5- xylene- 1- ol (15 g.) and aluminium chloride (9 g.) (1 mole) heated at 120 - 150° for 1½ hours gave colourless crystals of the ketone from ethanol (9.0 g.) (60%) m.p. 141 - 142°. Lit. - 143°.

Fission Treatment:-

5.0 g. Ketone with acetic (40 ccs.) and hydrobromic acid (20 ccs.) gave benzoic acid (2.10 g.) (78%) and 3:5-xylene- 1- ol (1.95 g.) (72%) m.p. 62 - 63° (and m.m.p.) after a twenty-four hour reaction time.

---

12. 2- Hydroxy- 4:6- dimethylacetophenone. Baddeley (loc.cit.)

This compound was prepared in the same way as the benzophenone derivative above. The acetate of the phenol gave a brown phenolic oil, with 1 mole aluminium chloride, which was distilled to give a main fraction boiling over the range 136 - 140° at 10 mms. This solidified to a pale yellow solid - stout needles from petrol ether (40 - 60°) m.p. 59 - 60°. Lit., 60°.

14.8 g. Acetate gave 6.50 g. ketone (45%).

A higher boiling fraction also gave a pale yellow solid m.p. 109 - 112° - needles from petrol ether (60 - 80°).

Analysis: Found: C - 70.0 ; H - 6.9

Required for a dimethyl hydroxy ketone: C - 73.2 ; H - 7.3

Required for a monomethyl " " : C - 70.2 ; H - 6.7

Action of Hydrobromic Acid on 2- hydroxy- 4:6- dimethylacetophenone:

A twenty-four hours' reflux of the ketone (3.0 g.) gave a phenolic solid (1.20 g.) which was recrystallised from petrol ether (40 - 60°) m.p. 59 - 61°. On mixing with the original ketone for a mixed melting point determination an oil was immediately produced. Mixed m.p. with 3:5- xylene- 1- ol gave no depression. Yield of 3:5- xylene- 1- ol - 54%.

13. 2- Hydroxy- 3:5- dimethylbenzophenone.

Reference: Meisenheimer et al., J. Prakt. Chem., 1928, 119, 338.

The benzoyl derivative of 2:4- xylene- 1- ol (yellow oil b.p. 110 - 112° at 15 mms.) (17.5 g.) gave a pale red complex with aluminium chloride (10.8 g. - 1 mole) after two hours at 130°. The resulting yellow oil was distilled to remove any unreacted benzoate and the fraction boiling at 206 - 208° at 20 mms., was collected (15.7 g.) (90%).

2:4- Dinitrophenylhydrazone - pale red needles from glacial acetic m.p. 282 - 284°.

Oxime - colourless crystals from aqueous alcohol m.p. 152 - 153°. Lit. 153 - 154°.

Hydrobromic Acid Treatment:-

The ketone, as expected, gave no fission products after seven hours treatment. The yellow reaction mixture however yielded benzoic acid (11%) (0.45 g. from 6.0 g. ketone) after twenty-four hours. The hydroxide extract gave a small amount of an oil - 3:5- dinitrobenzoyl derivative m.p. 162 - 164%. Lit., (for 2:4- xylene- 1- ol) - 164 - 165°.

The original ether extract of the diluted reaction mixture gave a yellow oil (4.53 g.) which was shown to be recovered ketone (oxime). Recovery - 76%.

---

14. 4- Hydroxy- 3:5- dimethylbenzophenone.

Reference: V. Auwers et al., Ann., 1930, 483, 44.

The benzoate (6.0 g.) of 2:6- xylene- 1- ol on treatment with aluminium chloride for two hours at 130 - 140° gave the ketone (3.92 g.) (65%) - colourless prisms from benzene m.p. 142 - 143°. Lit. 142° - 145°. (V. Auwers reported a 47% yield.)

Hydrobromic Acid Treatment:-

From a twenty-four hour reflux the ketone (2.0 g.) gave unchanged material (1.80 g.) - m.p. and m.m.p. (90%).

---

15. 2:4:6- Trimethylbenzophenone - Benzoylmesitylene.

Reference: Montagne, Rec. Trav. Chim. Pays Bas, 1908, 27, 355.

The ketone was obtained in good yield from a Friedel-Crafts reaction on freshly distilled mesitylene (24 g. - 28 ccs.), and benzoyl chloride (28 g. - 23 ccs.), in carbon disulphide solvent. The resulting yellow oil was fractionally distilled at 1.5 mms. to give the ketone.

Trinitro derivative: (Elbs, J. Prakt. Chem., 1887, 35, 488.)

Colourless needles from aqueous acetic acid m.p. 187 - 188°. Lit. 188°.

Hydrobromic Acid Treatment:-

The dark brown solution of the ketone (3.0 g.) gave a brown mobile oil which was high vacuum distilled b.p. 154 - 158° at 2 mms. to yield 2.72 g. starting material (identified by the trinitro derivative above).

SECTION II

pp. 60, 116

Hydrindene Series.

1. 5- Hydroxy- 6- acetylhydrindene.

Reference: Baker, J.C.S., 1937, 478.

The acetate of 5- hydroxyhydrindene (6.0 g.) with aluminium chloride (12.0 g.) in carbon disulphide (12 ccs.) gave a brown solution which, after the initial vigorous reaction had subsided, was heated for two hours on a water bath. The ether extract of the decomposed complex was extracted with sodium hydroxide which produced a yellow, insoluble, sodium salt. This was filtered off and acidified to yield an oil which quickly solidified - pale yellow prisms from methanol (2.80 g.) - 47% m.p. 58 - 59°. Lit., m.p. 59°.

Fission Treatment:-

(i) Seven Hours:

The yellow solution of the hydroxyketone (1.0 g.) in glacial acetic (20 ccs.) and hydrobromic acid (20 ccs.) soon changed to a dark red colour. It was diluted to give a brown oil and a small amount of red solid which was insoluble in the ether extract. This solid did not melt but darkened near 200°. It is probably a hydrobromic acid complex of some kind. (Yield 10 - 15 mgms.).

The ether solution was extracted with sodium hydroxide. The green alkali extract gave a brown oil

(0.40 g.) on acidification, which, with trituration in methanol and cooling, deposited colourless feathery needles (0.28 g.) m.p. 50 - 53°. Lit., m.p. for 5-hydroxyhydrindene 55°. Mixed m.p. - no depression.

Benzoyl Derivative: colourless plates from alcohol m.p. 107 - 108°.

Yield based on crystals obtained - 36%.

Yield based on oil recovered - 53%.

From the original ether extract pale yellow crystals were obtained (methanol) m.p. 55 - 57°. M.m.p. with starting ketone 56 - 57°.

Recovery of ketone - trace.

(ii) Twenty-four Hours:

The ketone (3.0 g.) gave an alkali soluble brown oil (2.13 g.) which was benzoylated in pyridine to yield the colourless derivative (2.05 g.) m.p. 106 - 107°.

Benzoylations of known weights of pure 5-hydroxyhydrindene gave, on an average, 90% yields of benzoylated phenol. On this basis a rough estimate of how much of the above oil (2.13 g.) was 5- hydroxyhydrindene was made and so the percentage yield of phenol was found (55%). 97%?/

---

2. 5- Hydroxy- 6- Benzoylhydrindene.

This ketone was prepared as above in a minimum of carbon disulphide. Reaction times were increased to twenty hours before a reasonable yield was obtained.

The benzoyl derivative of 5- hydroxyhydrindene (7.5 g.) gave a reddish brown viscous oil, which, after crystallisation from methanol (charcoal), yielded lemon yellow crystalline plates (1.60 g.) - 21% m.p. 107 - 108°. A mixed m.p. with the starting material gave a depression (20 - 30°). A dark green colour was obtained with ferric chloride in alcohol solution.

2:4- Dinitrophenylhydrazone: red needles from glacial acetic m.p. 235 - 236°.

Analysis: (i) Ketone. Found C - 81.1% ; H - 6.1%
Required C - 80.7% ; H - 5.9%

(ii) D.N.P. Found N - 13.8%
Required N - 13.1%.

Attempts to improve this yield of ketone using nitrobenzene as solvent at 100° and 150° gave no ketone. Larger volumes of carbon disulphide produced no ketonic material.

Hydrobromic Acid Treatment:-

The ketone (0.65 g.) gave (0.38 g.) - 58% starting material after a twenty-four hour reflux period. Benzoic acid (0.05 g.) (15%) was also produced (m.p. and m.m.p.).

3 & 4. 4- Hydroxy- 5- acetylhydrindene and 4- Hydroxy- 7- acetylhydrindene.

Reference: Baker et al., J.C.S., 1952, 1825.

Indan-4-ol + Derivatives

4- Hydroxyhydrindene was acetylated in the same was as the 5- isomer by shaking the sodium hydroxide solution of the phenol with acetic anhydride and extracting the non-phenolic portion with ether to give the acetylated compound in good yield (80%). A five hour treatment of this phenol ester (13.2 g.) with aluminium chloride (25 g.) and carbon disulphide (20 ccs.), on the water bath, gave

(4.30 g.) of the 4,7- isomer which was extracted from the ether extract of the decomposed complex with sodium hydroxide. Colourless elongated prisms from ethanol m.p. 185 - 186°. Lit., 185°.

2:4- Dinitrophenylhydrazone: red needles which could not be recrystallised because of its insolubility in most solvents. It was purified by repeated treatment with boiling ethanol - m.p. > 350°.

Analysis: (i) Ketone. Found C - 75.0 ; H - 6.8
Required C - 75.3 ; H - 7.0

(ii) D.N.P. Found N - 15.5
Required N - 15.7

After removal of the ether from the original extract, the residue was steam-distilled to give an oil (4.70 g.) which soon solidified to give colourless plates from methanol m.p. 45 - 47°. Lit. m.p. for 4- hydroxy- 5- acetylhydrindene 47°.

Hydrobromic Acid Treatment:-

a) 4- Hydroxy- 7- acetylhydrindene:

Seven Hour Reflux: Treatment of the ketone (0.5 g.) in the acid (15 ccs.) and glacial acetic acid (15 ccs.) gave a dark green solution. Most of the acid was distilled off, the solution diluted with water (30 ccs.) and then extracted with ether to give a brown oil. The oil was steam-distilled and the distillate yielded a colourless oil (0.22 g.) which solidified on seeding with 4- hydroxyhydrindene to a colourless solid which was recrystallised from petrol ether (40 - 60°) m.p. 47 - 49°.

M.m.p. 47.5 - 49°. Yield 38%. (Yield based on the oil obtained 58%.)

Extraction of the residue from the steam distillation with ether gave a trace of oil which solidified on standing and was crystallised from ethanol m.p. 175 - 180°.

This reaction was repeated for seven hours and the oil obtained converted into the aryloxyacetic acid - colourless needles from aqueous alcohol m.p. 182° (Kruber et al., Ber., 1939, 72B, 653). Standard preparations of the acid from known weights of 4- hydroxyhydrindene were made and thus the weight of 4- hydroxyhydrindene in the oil obtained from the reaction was calculated.

Yield of phenol based on aryloxyacetic acid - 50%.

Twenty-four Hour Reflux: This gave a yield of (0.26 g.) crystalline phenol from the ketone (0.88 g.) - 38%. Yield based on oil obtained - 59%.

Converting the oil from a similar reaction to the aryloxyacetic acid a yield of 50% 4- hydroxyhydrindene was calculated. Again a trace of starting material was obtained from these reactions.

b) 4- Hydroxy- 5- acetylhydrindene:

The ketone (0.50 g.) was refluxed for seven hours and the diluted reaction mixture steam distilled. A pale yellow residue was obtained which was filtered off, recrystallised from methanol and dried (0.08 g.) m.p. 42 - 44°. M.m.p. with starting ketone 42 - 45°. Recovery - 16%.

The distillate was extracted with ether to give (0.28 g.) of a phenolic oil which could not be crystallised. The

aryloxyacetic acid was prepared and the yield of 4-hydroxyhydrindene calculated from the yield of acid as before (65%).

Yield based on 0.28 g. oil recovered - 74%.

The residue from the steam distillate also gave an orange solid (10 mgms.) which was insoluble in the ether extract and which darkened and decomposed above 150°. Presumably it is a hydrobromic acid complex.

Twenty-four Hour Reflux: The ketone (1.12 g.) gave 0.18 g. solid on steam distillation which again proved to be starting material m.p. and m.m.p. (16%). The distillate, on ether extraction also yielded 0.65 g. of a yellow oil which crystallised from petrol ether (40 - 60°) on standing (0.55 g.) m.p. 42 - 45°. When mixed with the starting ketone immediate melting took place but a mixed m.p. with 4- hydroxyhydrindene gave 43 - 45°.

Yield based on 0.65 g. oil - 77%

Yield based on 0.55 g. crystals - 65%

Yield from aryloxyacetic acid from a similar reaction - 71%

Again from this reaction the residue from the steam distillation yielded a small quantity (10 - 15 mgms.) of the complex mentioned above.

SUMMARY OF RESULTS:

Ketone	Reaction Time (hrs.)	% Yield of Phenol			% Recovery of ketone
		Based on oil recovered	Based on crystals	Based on aryloxy deriv.	
1. 5- hydroxy- 6- acetylhydrindene	7	53	36		Trace
	24	93		55 (benzoyl deriv.)	Trace
2. 5- hydroxy- 6- benzoylhydrindene	24	15 per cent Benzoic Acid			58
3. 4- hydroxy- 7- acetylhydrindene	7	58	38	50	Trace
	24	59	38	50	Nil
4. 4- hydroxy- 5- acetylhydrindene	7	74		65	16
	24	77	65	71	16

SECTION II

Naphthalene Series

1. 1- Benzoyl- 2- methoxynaphthalene.

Reference: Woodham, Thesis Edin., p. 88 and 144.

This ketone was prepared by a Friedel-Crafts reaction of β - naphthyl methyl ether (15 g.) in s-tetrachlorethane at 25°. After removal of the solvent by steam distillation the yellow oil obtained was distilled above 360° at atmospheric pressure to give a yellow solid (16.5 g.). Sodium hydroxide extraction gave 0.5 g. (3%) of 1- benzoyl- 2- hydroxynaphthalene m.p. 136 - 138°. Lit. m.p. 141°. The remaining solid gave colourless prisms from petrol ether (100 - 120°) of 1- benzoyl- 2- methoxynaphthalene (14.5 g.) 58% m.p. 122 - 124°. Lit., m.p. 126°.

Fission Treatment:-

The ketone (5.0 g.) was given a seven hour reflux with glacial acetic acid and hydrobromic acid. On dilution of the mixture with water a pinkish solid settled out, which was extracted into ether and the ether extract in turn extracted with (i) sodium carbonate - giving benzoic acid (1.50 g.) - 65%.

(ii) sodium hydroxide - giving β - naphthol (2.25 g.) - 80%.

The products were identified by m.p. and m.m.p. and the ferric chloride test.

2. 1- Benzoyl- 2- hydroxynaphthalene.

β - naphthyl benzoate (5.0 g.) was treated with aluminium chloride (5.0 g.) in s- tetrachlorethane (20 ccs.) at 100 - 120° for 2½ hours. After decomposing the complex with ice and hydrochloric acid the aqueous solution was extracted with ether-benzene. The sodium hydroxide extract of this gave an oil (3.0 g.) which, after treatment with charcoal, was recrystallised from alcohol. It was evident that a mixture of brown and yellow solids was present. The separation was effected by their different solubilities in petrol ether (80 - 100°) - the yellow solid being much more soluble. Recrystallisation of the yellow solid produced microcrystalline yellow needles m.p. 132 - 134°. Yield - 0.6 g. (12%).

As a result of this small yield another method of preparation was attempted applying the evidence that often in Friedel-Crafts reactions, involving methyl ethers, demethylation occurs. The reaction detailed in (1) above was repeated but the mixture was heated at 100° for eight hours or longer. With this treatment it was found that the percentage of hydroxy ketone formed had risen to 40%.

Hydrobromic Acid Treatment:-

This ketone gave results similar to those obtained for the corresponding methyl ether above.

---

3. 1- Acetyl- 2- hydroxynaphthalene.

Reference: Braun and Witt, Ber., 1914, 47, 3216.

β - naphthyl methyl ether (10.0 g. - 1 mol.),

acetyl chloride (5.0 g. - 1 mol.) and aluminium chloride (11.9 g. - 1.4 mols.) in dry benzene gave a yellowish complex which gradually dissolved to produce a green solution. After 2½ hours gentle heating the complex was decomposed as usual and the benzene layer washed with water, extracted with sodium carbonate and caustic soda. The caustic extraction gave a yellow sodium salt which, on acidification, deposited a yellow oil. This was solidified by trituration in water - yellow rhombs from petrol ether (60 - 80°) (5.2 g.) m.p. 63 - 64°. Lit. - 64° (41%).

The original benzene solution provided a colourless solid - recrystallised from petrol ether (60 - 80°) m.p. 105 - 107°. Lit. for 1- acetyl- β - naphthyl acetate - 107°. Yield - 1.20 g.

This ketone was also prepared by the Fries reaction on β - naphthyl acetate (Fries, Ber., 1921, 54, 711), but the yields were small by this method (25 - 30%). The product was mainly starting ester. The use of aluminium bromide gave no improvement in the yield of ketone.

Fission Treatment:-

The methyl ketone (2.0 g.) after a seven hours' reflux gave colourless crystals of β- naphthol - 1.10 g. (68%) from water m.p. 121 - 122°. M.m.p. - no depression.

Ferric chloride test (i) β - naphthol - green colour in alcohol.

(ii) Ketone - dark red colour in alcohol.

---

4. 1- Benzoyl- 4- methoxynaphthalene.

Reference: Fierz-David and Jaccard, Helv. Chim. Acta, 1928, 11, 1042.

α- Naphthyl methyl ether (13.0 g.) (from α- naphthol in 60% yield by methylation with dimethyl sulphate) in s-tetrachorethane (175 ccs.) was treated with benzoyl chloride (12 g.) and aluminium chloride (12 g.). The resulting brown oil was distilled under high vacuum to give a green oil which, on trituration with petrol ether (80 - 100°), deposited lemon green needles m.p. 82 - 83°. Lit., - 83°. Yield - 12.5 g. (64%).

Hydrobromic Acid Treatment:-

1- Benzoyl- 4- methoxynaphthalene (2.0 g.) was refluxed for seven hours with excess of the reagent mixture. A colourless phenolic solid (0.60 g.) m.p. 91 - 93° was obtained, which gave no m.p. depression when admixed with α - naphthol. Yield of α- naphthol - 60%.

Benzoic acid was also found (0.43 g.) - 41%.

---

5. 1- Benzyl- 2- methoxynaphthalene.

Reduction of the corresponding ketone (3.0 g.) by the Clemmensen method yielded a viscous oil. This was treated with charcoal in acetone solution, the acetone removed and replaced with benzene from which a sticky colourless solid crystallised out. This solid, after washing with cold ether and recrystallisation from benzene, had m.p. 79 - 82°. Yield - 1.20 g. (40%).

Analysis: Found. C - 86.7; H - 6.3
Required. C - 87.1; H - 6.4

Hydrobromic Acid Treatment:-

A seven hour treatment of the methyl ether (0.50 g.) produced a colourless solid which recrystallised as colourless needles from petrol ether (60 - 80°) m.p. 112 - 113°. Lit., m.p. for 1- benzyl- 2- hydroxynaphthalene 112 - 115°. Yield - 0.25 g. (52%).

---

6. 1- Benzyl- 4- hydroxynaphthalene.

The 1- benzoyl- 4- methoxy ketone (3.0 g.) in glacial acetic (50 ccs.) was added to zinc (30 g.), /previously treated with mercuric chloride (3 g.) and concentrated hydrobhloric acid (2 ccs.) in water (50 ccs.) /hydrochloric (35 ccs.), and water (15 ccs.). Toluene was added to provide an organic layer, and the reaction mixture was refluxed for thirty hours. The toluene layer was separated and dried over sodium sulphate. The toluene was removed under vacuum and lemon yellow crystals (2.30 g.) were obtained from petrol ether (80 - 100°) m.p. 123 - 125°. Lit. m.p. for 1- benzyl- 4- hydroxynaphthalene 125 - 126°.

Demethylation had occurred during the reduction.

Hydrobromic Acid Treatment:-

The ketone (1.0 g.) was refluxed as usual and the diluted solution deposited reddish plates (0.7 g.) m.p. 105 - 112°. After several recrystallisations from petrol ether the m.p. was raised to 120 - 123°. M.m.p. 118 - 121° (with starting phenol.)

Recovery of starting material 60 - 70%.

7. 2- Benzoyl- 3- hydroxynaphthalene.

Reference: C.A., 1929, 2187.

2- Hydroxy- 3- naphthoic acid was methylated with dimethyl sulphate (Holt et al., J.C.S., 1931, 374) in good yield and the acid chloride was prepared by treating the methoxy acid (6.0 g.) in dry ether (20 ccs.) with a slight excess of thionyl chloride and heating on a water bath for three hours.

The acid chloride, dissolved in dry benzene (50 ccs.), was added slowly (30 mins.) to a well stirred mixture of aluminium chloride (5.25 g.) and benzene (50 ccs.). A red solid settled out and the stirred mixture was kept at 70 - 80° for twelve hours, during which a constant evolution of hydrochloric acid gas was noticed. The complex was decomposed (ice and hydrochloric acid) and by heating on the water bath all the solid material was dissolved in the benzene layer which was separated and washed with water. Sodium carbonate extraction removed unreacted acid (a trace was found). After washing with water the benzene solution was finally dried and the benzene removed to give a red solid which was treated with charcoal in acetone. The resulting yellowish solid was recrystallised from benzene m.p. 159 - 161°. Lit., 161 - 162° for 2- benzoyl- 3- hydroxynaphthalene. Yield - 60%.

2:4- Dinitrophenylhydrazone (by Brady's method):-
Orange microcrystalline solid from tetralin m.p. 315 - 318°

Analysis: (i) Ketone - Found. C - 83.2; H - 4.9
Required. C - 82.5; H - 5.15
(ii) D.N.P. - Found. N - 12.9
Required. N - 13.1

Again demethylation has occurred during the Friedel-Crafts reaction.

Reaction with Hydrobromic Acid:-

The hydroxy ketone (0.5 g.) was found to be very slowly soluble in glacial acetic acid and a large excess of the mixture had to be used (50 ccs. acetic with 20 ccs. acid). Only after ten hours boiling had all the ketone dissolved, during which the original yellow solution had changed to a very dark brown colour. The reaction time was twenty-four hours. After removal of some of the acetic acid by distillation, yellow crystals settled out. The diluted solution was then extracted with ether and the ether subsequently treated with (i) sodium carbonate (which gave no benzoic acid on acidification) and (ii) caustic soda. The caustic extract yielded an oily yellow solid which was recrystallised from xylene to give microcrystalline yellow needles (0.40 g.) m.p. 158 - 162°. M.m.p. with starting ketone - 159 - 161°. D.N.P. 316 - 318°.

Recovery of starting material - 80%.

---

8. 2- (p- Methoxybenzoyl)- 3- hydroxynaphthalene.

Reference: C.A., 1929, 2187.

The hydroxy acid chloride (20.0 g.) of 2- hydroxy-3- naphthoic acid /from thionyl chloride in dry petrol ether (60 - 80°)/ in nitrobenzene (50 ccs.) was added slowly to a mixture of anisole (10.8 g.) and aluminium chloride (13 g.) over a period of one hour. The solutions were cooled in ice during the addition. A red complex was

immediately formed and the mixture was stirred for sixteen hours at room temperature. Decomposition of the complex, followed by removal of the solvent by steam distillation, produced a yellow oil which was dissolved in ether and extracted with carbonate and sodium hydroxide. The hydroxide extract gave a yellow solid on acidification which was recrystallised from alcohol (charcoal) - microcrystalline yellow needles (22.0 g.) m.p. 132 - 134°. Lit., - 134°. Yield 75%.

2:4- Dinitrophenylhydrazone:- red plates from tetralin m.p. 290 - 293°.

Analysis: (i) Ketone - Found. C - 78.0 ; H - 4.8
Required. C - 78.0 ; H - 4.8
(ii) D.N.P. - Found. N - 12.6
Required. N - 12.9

Hydrobromic Acid Treatment:-

(a) Seven Hours Reflux: The orange ketone (6.0 g.) was allowed to cool and a yellow solid crystallised out (5.80 g.). This was dissolved in ether and extracted with

(i) sodium carbonate - yellow solid (0.3 g.) on acidification - crystals from benzene m.p. 211 - 214°

(ii) sodium hydroxide - red oil on acidification - yellow plates from benzene (4.90 g.) m.p. 130 - 133°.

D.N.P. - 290 - 292°.

This was recovered starting material. The acidic portion was thought to be 2- hydroxy- 3- naphthoic acid m.p. 222 - 223° but a mixed m.p. determination gave a depression to 198 - 205°. So this compound was not 2-

hydroxy- 3- naphthoic acid but it could have some of this acid admixed (see below). Recovery of original ketone - 82%.

(b) Twenty-four Hours Reflux: From the ketone (5.20 g.) the same yellow solid (4.80 g.), soluble in carbonate, was obtained m.p. 204 - 205°. The solid however gave a D.N.P. m.p. 315 - 317° from tetralin and so the original ketone has merely been demethylated.

The solubility of the ketone in carbonate is due to the presence of two hydroxyl groupings in the molecule after demethylation.

(c) To establish definitely whether there was any 2- hydroxy- 3- naphthoic acid present in the carbonate extract, several paper chromatograms were run using a saturated sodium chloride - n- butanol - pyridine solvent mixture. The method employed was that of capillary ascent of the organic phase. 2- Hydroxy- 3- naphthoic acid, phenol and the starting ketone were spotted separately on Whatman No. 41 paper. Beside this a mixture of all three and a separate spot containing the carbonate soluble material were developed. The development time was twenty-four hours. A good separation of starting ketone and 2- hydroxy- 3- naphthoic acid was obtained from the mixture although phenol could not be identified under ultra-violet light. The solid from the reaction mixture did not separate and no spot corresponding to 2- hydroxy- 3- naphthoic acid was found.

---

9. 1- Hydroxy- 4- naphthylideneacetophenone.

Reference: Hill and Melhuish, J.C.S., 1935, 1161.

1- Hydroxy- 4- naphthaldehyde was prepared in good yield according to the method of Adams and Levine (J.A.C.S., 1913, 45, 2377), by passing hydrochloric acid gas through a well stirred solution of crude α- naphthol and fused zinc chloride in dry ether for two hours.

The aldehyde (8.5 g.) was added to a solution of 50% ethanol (90 ccs.) containing acetophenone (6.5 g.) and potassium hydroxide (22.5 g.). The solution was heated at 95 - 100° for an hour and a half during which it became deep red in colour.

It was cooled, acidified and extracted with ether (3 x 30 ccs.). The ether in turn was shaken with sodium hydroxide (3 x 15 ccs.) leaving any unreacted acetophenone in the organic layer. Acidification of the alkaline extract gave a brownish solid which was treated with charcoal in alcohol to give brownish yellow needles on recrystallisation (2.60 g.) m.p. 216 - 217°. Yield - 20%.

Analysis: (i) Ketone - Found. C - 82.6; H - 5.1
Required. C - 83.2; H - 5.1

(ii) 2:4- Dinitrophenylhydrazone -
Found. N - 11.4
Required. N - 12.3

Hydrobromic Acid Treatment:-

The chalkone (1.55 g.) was dissolved in glacial acetic acid (30 ccs.) and on addition of hydrobromic acid (20 ccs.)

the solution immediately turned red in colour. After seven hours reflux the diluted solution deposited a brownish red solid which was insoluble in ether but soluble in chloroform. Extraction with the latter yielded a deep purple solution which was shaken up with:-

(i) Carbonate - no acidic material.

(ii) Sodium hydroxide - on acidification a red oil was produced which eventually solidified to a solid m.p. 91 - 93°. M.m.p. with α - naphthol - no depression.

Yield - 0.12 g. (14%).

The original chloroform solution was dried over sodium sulphate and the solvent removed to leave a glistening purple solid (0.84 g.) which was soluble in glacial acetic acid but practically insoluble in alcohol (pale red solution). This was chromatographed with chloroform as solvent to give a recovery of 0.80 g. It was probably a compound formed between the unsaturated side chain which has been split off and hydrobromic acid or possibly a polymeric compound formed from the side chain. It was not investigated further.

---

10. 2- Hydroxy- 1- naphthylideneacetophenone.

(a) Naphthaflavylium chloride - Hill and Melhuish (loc. cit.).

To 2- hydroxy- 1- naphthaldehyde (5.0 g.) (from β - naphthol as above) in dry alcohol (25 ccs.) acetophenone (3.5 g.) was added and dry hydrochloric acid gas passed through the solution for three hours with cooling in an ice/

salt mixture. On standing for twenty hours a brown solid settled out which was filtered off - (9.25 g.) m.p. 120 - 124° which is the required chloride.

(b) 2- Phenylnaphthapyranol- 4- ethyl ether.

The chloride (5.0 g.) was dissolved in alcohol (100 ccs.) and 10% sodium hydroxide (50 ccs.) added. After standing for twenty-four hours a white solid (2.0 g.) settled out from the red solution. It recrystallised from petrol ether (40 - 60°) as colourless needles m.p. 130 - 133°. Lit., 131 - 133°. A further portion of the ether (0.49 g.) was obtained on acidification of the alkaline reaction mixture. Total yield - 2.4 g.

The ether (2.0 g.) was heated under reflux with alcohol for thirty minutes to give the unsaturated ketone (1.80 g.) as a brownish yellow solid - needles from aqueous alcohol m.p. 143 - 144°.

Hydrobromic Acid Treatment:-

The reddish coloured solution of the ketone (0.30 g.) in glacial acetic (15 ccs.) and hydrobromic acid (15 ccs.) was refluxed for seven hours. On dilution of the cooled reaction mixture, a chocolate brown solid was precipitated which, after treatment with charcoal, gave yellowish green crystals from dilute alcohol m.p. 129 - 135°. M.m.p. with starting ketone 127 - 137°. This seemed to be impure starting material. It was steam distilled but no β-naphthol was found in the distillate. The original reaction mixture was also steam distilled but again no β- naphthol was obtained. On cooling the reaction mixture, orange crystals (0.10 g.) settled out m.p. 188 - 192°.

This treatment was repeated for twenty-four hours using 0.24 g. ketone and the reaction mixture was diluted and extracted with ether. The brown solid which had settled out was insoluble in ether. The ether extract gave no solid.

The brown solid (0.18 g.) was filtered off and recrystallised from water and a little hydrobromic acid (10%) - the material being insoluble in pure water - to give orange brown needles m.p. 188 - 191°.

Lassaigne test - positive for bromine

Analysis: Found Br - 20.0

Required Br - 22.6 for naphthaflavylium bromide ($C_{19}H_{14}O_2Br$)

The compound was soluble in boiling caustic soda to give a red solution.

---

11. 1- (2';3'- dimethoxybenzoyl)- naphthalene.

(a) 2';3'- dimethoxyphenyl- 1- naphthylcarbinol.

α - Naphthylmagnesium bromide was prepared from α - bromonaphthalene (11.8 g.) and magnesium (1.50 g.) in dry ether (50 ccs.).

2:3- Dimethoxybenzaldehyde (10.0g.) was added slowly in dry ether (25 ccs.) to the stirred Grignard solution and the reaction mixture was stirred for fifteen hours at room temperature. It was finally heated for two hours under reflux and decomposed by pouring on to ice and dilute sulphuric acid. The ether layer was separated, washed with water and dried over sodium sulphate. On removal of the

solvent a colourless solid was obtained which recrystallised from benzene-petrol ether (60 - 80°) or methanol as elongated prisms m.p. 132 - 134°. Yield - 8.80 g. (52%).

Analysis: Found C - 77.7 ; H - 6.2
Required C - 77.6 ; H - 6.1
(for $C_{19}H_{18}O_3$)

(b) Oxidation of the Secondary Alcohol.

i) Sodium Dichromate:- The alcohol (0.5 g.) was dissolved in glacial acetic acid (20 ccs.), which had been redistilled from potassium permanganate, and a slight excess of dichromate added. After heating for thirty minutes the mixture was poured into water and the whole extracted with ether (3 x 20 ccs.). The ether was well washed with water and carbonate to remove any acetic acid and the solvent removed to give an impure oil (0.35 g.) which could not be crystallised. However it gave a dinitrophenylhydrazone m.p. 293 - 295°.

The oil was chromatographed with petrol ether as solvent and a colourless eluate yielded a yellow oil which recrystallised from absolute alcohol (charcoal) as colourless rhombs m.p. 79.5 - 80.5°. Yield 0.10 g. - 20%.

Analysis: Found C - 77.6 ; H - 5.5
Required C - 78.0 ; H - 5.5
(for $C_{19}H_{16}O_3$)

The oxidation was repeated in the cold for two hours but again the alcohol only gave a 20% yield of ketone.

ii) Chromic Oxide:- The alcohol (0.50 g.) with chromic oxide (1.0 g.) when heated gently for thirty minutes

in glacial acetic acid, gave the ketone (0.13 g.) which solidified on standing.

iii) Aluminium Isopropoxide:- To the alcohol (1.0 g.) in dry benzene (100 ccs.), acetone (50 ccs. - 200 mols.) and aluminium isopropoxide (0.7 g. - 3 mols.) were added. The pale yellow cloudy solution was refluxed for twenty-four hours. On cooling, the solution was shaken with dilute sulphuric acid, washed with water, dried and the solvent removed to give a colourless solid (0.75 g.) which proved to be the starting material.

iv) Aluminium t-Butoxide:- The alcohol (1.0 g. - 1 mole.) was refluxed with cyclohexanone (1.10 g. - 3 moles.), and aluminium tertiary-butoxide (1.0 g. - 3 moles.) in sodium dried, sulphur free, xylene (50 ccs.) for fifteen hours. The solution became deep yellow after three hours. It was worked up as above to give the starting carbinol (0.65 g.)

This oxidation was repaated with cyclohexanone as the hydrogen acceptor but a reaction time of sixty hours was employed. 0.5 g. Alcohol gave a recovery of 0.45 g.

With benzil as acceptor and a reaction time of twenty-four hours the alcohol (0.5 g.) gave a little ketone material (0.05 g.) (m.p. and m.m.p.).

The chromic acid method of oxidation was used in a large scale oxidation of the carbinol (4.4 g.) to give the ketone (0.92 g.) which was purified by chromatography as before.

Yield - 21%.

Hydrobromic Acid Treatment:-

The ketone (0.50 g.) was refluxed for seven hours, the solution changing from yellow to dark brown in this time. The ether extract of the diluted reaction mixture was itself extracted with:-

(i) Carbonate - no solid material on acidification and ether extraction.

(ii) Sodium hydroxide - dark oil (0.32 g.) which went solid on trituration with alcohol.

The oil gave yellow needles on crystallisation from benzene m.p. 148 - 151° (0.22 g.).

The phenolic solid, in alcohol, gave a green colour with ferric chloride.

Analysis: Found. C - 77.2 ; H - 4.8
Required. C - 77.2 ; H - 4.6
(for $C_{17}H_{12}O_3$)

The product from the reaction is therefore the demethylated starting ketone.

---

12. 1- (2':4':6'- trimethylbenzoyl)- naphthalene.

The acid chloride of α- naphthoic acid (1.95 g.) (from the acid and phosphorous pentachloride without solvent) was dissolved in nitrobenzene (20 ccs.) and slowly added to a stirred solution of mesitylene (1.2 g.) and aluminium chloride (1.5 g.) in nitrobenzene (20 ccs.). The resulting green solution was allowed to stand at room temperature overnight, decomposed as usual and the solvent removed by steam distillation. On cooling, the solution deposited pale yellow crystals (2.4 g.). These were

dissolved in ether and extracted with carbonate to give a little α - naphthoic acid (0.24 g.). The ether solution was dried over sodium sulphate and the solid obtained was recrystallised from petrol ether (100 - 120°) - pale yellow prisms m.p. 158 - 159.5°.

Yield - 1.84 g. (60%).

This compound would not give a dinitrophenylhydrazone derivative by the Allen or Brady methods even when reflux times up to two hours were used.

Analysis: Found. C - 86.8 ; H - 6.7
Required. C - 87.6 ; H - 6.5
(for $C_{20}H_{18}O$)

Hydrobromic Acid Treatment:-

(i) Seven Hour Reflux:- The ketone (0.5 g.) was difficultly soluble in glacial acetic acid so a good excess was used with hydrobromic acid (30 ccs.). Yellow crystals settled out, on cooling the reaction mixture, and these were filtered off and washed with water (0.43 g.) m.p. 158 - 159°. M.m.p. with starting material 156 - 158°. The compound was recrystallised from glacial acetic acid.

Recovered ketone - 84%.

(ii) Twenty-four Hour Reflux:- This gave an 80% recovery of the original ketone.

66

13. 5:8- Dimethoxy- α - tetralone.

p.74

The starting material used was hydroquinone dimethyl ether which was prepared in 93% yield by methylation of the phenol with dimethyl sulphate (Bogert and Howells, J.A.C.S., 1930, 52, 840).

a) 2:5- Dimethoxybenzoylpropionic acid:-

The ether (16.6 g.) and succinic anhydride (12 g.) were dissolved in nitrobenzene (50 ccs.) and aluminium chloride added in small amounts (4 x 0.7 g.) over thirty minutes. After standing at room temperature for forty-eight hours, the reaction mixture was decomposed with ice and dilute hydrochloric acid and the solvent removed by steam distillation. The solid material left was extracted with ether which was in turn extracted with carbonate. The brown carbonate solution (100 ccs.) was treated with charcoal for thirty minutes, filtered and acidified on cooling to give a brown solid (24 g.) m.p. of crude material 100 - 103°. Lit. 107°.

b) 2:5- Dimethoxyphenylbutyric acid:-

Clemmensen reduction of the crude keto acid with amalgamated zinc and hydrochloric acid for thirty hours gave a brown oil from the toluene layer (15.5 g.) - 80%.

c) Ring closure to 5:8- dimethoxy- α-tetralone:-

Phosphoric acid (300 g.) and phosphorous pentoxide (280 g.) were heated on a water bath for fifteen hours the mixture being protected from moisture by a calcium chloride tube. The butyric acid (6.50 g.) was added to the resulting solution and the heating continued at 100° for thirty minutes. After allowing the red solution to cool it was poured into a mixture of ice and water (700 g.) and the whole extracted with ether (3 x 50 ccs.). This ether extract yielded a small amount of

a sticky solid material from the carbonate extraction. Sodium hydroxide extraction showed, by the absence of any organic material on acidification, that no demethylation had occured during cyclisation.

Removal of the ether, after drying, gave a brown oil (4.50 g.) which was chromatographed on an alumina column (30 x 1 cms.). The oil was added in benzene solution and subsequent development carried out with a mixture of benzene and petrol ether (60 - 80°) (1:1).

Several fractions were collected:-

Fraction i) Colourless eluate - (blue fluorescence under ultra-violet light.) Removal of the solvent gave a small amount (0.20 g.) of a colourless oil which could not be crystallised.

ii) Pale Yellow eluate - this gave pale yellow crystals on standing m.p. 58 - 60° which were recrystallised from benzene - petrol ether (60 - 80°) m.p. 59 - 60° (4.03 g.). Yield - 68%.

2:4- Dinitrophenylhydrazone: an immediate copious red precipitate was obtained which recrystallised from glacial acetic acid as bright red needles m.p. 234 - 235°.

Analysis of ketone and D.N.P.

i) Ketone: Found C - 70.4 ; H - 6.7
Required C - 69.9 ; H - 6.8
(for $C_{12}H_{14}O_3$)

ii) D.N.P.: Found N - 14.7
Required N - 14.5

Attempted Fission of the Tetralone derivative.

The ketone (0.30 g.) was treated as usual with excess

of reagent and the solution boiled for twenty-four hours. The ether extract of the diluted solution was extracted with i) Carbonate - a trace of material was obtained which could not be solidified.

ii) Sodium Hydroxide - acidification gave a lemon yellow solid (0.20 g.) m.p. 183 - 184°, - crystals from aqueous alcohol.

D.N.P. - red needles from dilute acetic acid m.p. 278 - 280°. The oil from the carbonate extract also gave this D.N.P. derivative suggesting that this compound recovered is the corresponding 5:8- dihydroxy-α - tetralone (the solubility in carbonate being due to the presence of the two hydroxyl groupings).

Analysis: i) Ketone: Found C - 67.8 ; H - 5.6
Required C - 67.4 ; H - 5.6
(for $C_{10}H_{10}O_3$)

ii) D.N.P.: Found N - 15.3
Required N - 15.6

---

14. 1- Benzoyl-β - naphthyl phenyl ether.

a) β - Naphthyl phenyl ether.

Reference: Ullmann and Sponagel, Ann., 1906, 350, 92.

β - Naphthol (30 g.) was added to caustic potash (10.5 g.) and the solid mixture heated to 200° on an oil bath for thirty minutes to ensure the complete removal of water. Bromobenzene (24 g.) was added and the temperature raised to 240° for two and a half hours after the addition of 0.1 - 0.15 g. copper bronze catalyst. The dark reaction mass was distilled under high vacuum and several fractions

were collected:-

i) Unchanged bromobenzene

ii) " β - naphthol

iii) Phenyl ether as a colourless solid (3.80 g.)

m.p. 44 - 46°. Lit. 45°.

This method was very crude and yields of the ether were very poor.

b) 1- Benzoyl- β - naphthyl phenyl ether.

The ether from a) (3.8 g.) was dissolved in carbon disulphide (25 ccs.) and aluminium chloride (2.1 g.) added. Benzoyl chloride (2.49 g.) in carbon disulphide (15 ccs.) was slowly dropped in and the red solution was well stirred, left at room temperature overnight, and then heated gently for two hours. After decomposing the complex with ice and hydrochloric acid, followed by gentle heating on a water bath, the organic layer was separated and the aqueous layer extracted with ether. The two organic layers were then combined and extracted with carbonate. A little benzoic acid was recovered. Sodium hydroxide extraction gave no organic material.

The ether-disulphide mixture was washed well with water, dried and the solvent removed. The red oil obtained could not be crystallised (4.50 g.). Neither a dinitrophenylhydrazone nor an oxime could be prepared.

The oil was chromatographed in benzene-petrol ether (60 - 80°) to give a pale yellow viscous oil which failed to crystallise.

Analysis: Found C - 84.1 ; H - 5.1
Required C - 85.2 ; H - 5.0
(for $C_{23}H_{16}O_2$)

Distillation of this oil gave a colourless solid which melted at 35 - 38° but which analysed reasonably well for β - naphthyl phenyl ether.

On standing in the refrigerator for two months the oil showed signs of crystallising, a few colourless crystals appearing.

Hydrobromic Acid Treatment:-

The oil from the above reaction (0.60 g.) was treated in glacial acetic acid (25 ccs.) and hydrobromic acid (15 ccs.) for three hours. After most of the acetic acid had been removed, the remainder was poured into water (50 ccs.) and a yellow emulsion was formed. This was extracted with ether (3 x 20 ccs.), washed and the ether extracted with:-

i) Carbonate - yellowish solution on acidification which, on extraction with ether and removal of the solvent, gave a trace of colourless solid m.p. 112 - 116°. Recrystallised from water m.p. 116 - 119°. M.m.p. with benzoic acid 118 - 120°.

ii) Sodium hydroxide - trace of phenolic solid on acidification and extraction. The solid was oily and could not be recrystallised. It melted over the range 85 - 105° and was probably β - naphthol.

The original ether solution was washed and dried. It gave a reddish oil (0.38 g.) which showed signs of crystallisation on cooling in a cardice/acetone mixture. The oil was chromatographed on a column (30 x 0.5 cms.) and eluted with benzene-ethyl acetate (5%) to give a yellowish red oil

which crystallised, on standing, as colourless stout prisms m.p. 165 - 168°. Recovery - 0.22 g. Recrystallisation, after charcoal treatment, gave prisms from petrol ether (60 - 80°) m.p. 169 - 171° which were analysed, (see below).

The alumina column was stripped with a benzene-ethyl acetate mixture (1:1) to yield a dark yellow oil which crystallised on standing (0.08 g.) m.p. 166 - 170° and is apparently the same compound as that melting at 169 - 171° (M.m.p. - no depression).

The colourless solid gave no D.N.P. derivative (Brady and Allen methods) and contained no bromine (Lassaigne Test).

Analysis: Found C - 84.4 ; H - 5.2
Required C - 85.2 ; H - 5.0
(for starting material)
$C_{23}H_{16}O_2$

This compound is therefore the starting material. A repeat of this reaction for five hours gave the same colourless solid with a trace of benzoic acid and a trace of impure phenolic material.

After twenty-four hours treatment the solid was still recovered in 70 - 75% yield with the usual trace of benzoic acid and a phenolic portion which was identified as β-naphthol by steam distillation m.p. 112 - 116°. M.m.p. 115 - 118°.

Phosphoric Acid Treatment of the Ketone:-

Treatment of the oil with phosphoric acid in glacial acetic acid was carried out for twenty-four hours. The oil (0.92 g.) in a mixture of phosphoric (10 ccs.) and glacial acetic (30 ccs.) gave a dark red solution which

was worked up in the usual way. The diluted reaction mixture yielded a trace of benzoic acid (.10 mgms.) and a little oily phenolic material which crystallised on standing and gave m.p. 110 - 116°. M.m.p. 110 - 114°.

This is presumably some impure β - naphthol again.

---

15. Treatment of 1- Benzoyl- 2- methoxynaphthalene with other reagents.

a) Phosphoric Acid.

i) On β- naphthyl methyl ether:- Excess pure phosphoric was refluxed with the methyl ether (1.50 g.) for seven hours. β - Naphthol (1.10 g.) and a little ether (0.15 g.) were recovered.

With a concentration of one part phosphoric acid to 3 or 4 parts glacial acetic acid no demethylation occurred when 4.0 g. of methyl ether were treated for the same time. The ether (3.70 g.) was recovered.

ii) On 1- benzoyl- 2- methoxynaphthalene:- The ketone (1.0 g.)was refluxed with a mixture of glacial acetic acid (35 ccs.) and phosphoric acid (8 ccs.) for seven hours. The ether extract of the diluted solution was extracted with A) Sodium Carbonate - benzoic acid (0.34 g.) - 74% - was obtained on acidification.

B) Sodium Hydroxide - β - naphthol (0.30 g.) - 55%.

The original ether solution gave a brown oil which crystallised on seeding with β- naphthyl methyl ether (0.13 g.) - 20% m.p. 69 - 71°. M.m.p. 68 - 72°.

This reaction was repeated using phosphoric acid (4 ccs.) in acetic acid (35 ccs.) and after seven hours no β - naphthol was recovered. The methyl ether m.p. 70 - 72° was obtained in 62% yield.

b) Sulphuric Acid.

1- Benzoyl- 2- methoxynaphthalene (1.0 g.) was dissolved in glacial acetic acid (20 ccs.) and concentrated sulphuric acid (1 cc.) was slowly dropped into the solution with frequent shaking. The pale orange solution was refluxed for thirty minutes to give benzoic acid (0.20 g.) - 44% - and a neutral fraction which was chromatographed in benzene-petrol ether (60 - 80°) (1:1) on a neutral alumina column (25 x 1 cms.) to yield colourless crystals (0.30 g.) - 46% m.p. 70 - 72°. M.m.p. - no depression (with β - naphthyl methyl ether).

c) Dichloracetic Acid and Hydrobromic Acid.

To correlate treatments with this acid and acetic acid the reactions were carried out at the same reflux temperature (118 - 120°) in an oil bath.

The ketone (3.50 g.) was dissolved in dichloracetic (20 ccs.) and hydrobromic acid (15 ccs.) added. The dark red solution was heated on an oil bath for one hour and worked up as usual. Benzoic acid (38%) and β - naphthol (48%) were produced.

By comparison, similar treatment for one hour using 3.50 g. ketone, glacial acetic acid (20 ccs.) and hydrobromic acid (15 ccs.) gave benzoic acid (20%) and β - naphthol (16%). The starting ketone was recovered from

the neutral ether extract (1.60 g.) - 46%. So the reaction is faster with the stronger dichloracetic acid.

SECTION IV

Phenanthrene Series, etc.

1. 9- Hydroxy- 10- benzoylphenanthrene.

a) 9- Methoxyphenanthrene.

Reference: Fieser at al., J.A.C.S., 1936, 58, 2163.

Attempts to prepare this compound by the bromination method of Fieser gave very small yields of 9-hydroxyphenanthrene and the method of Schultz et al., J.A.C.S., 1940, 62, 2902 was therefore used.

Freshly distilled fluorenone (32.0 g.) was dissolved in pure diethyl ether (d. 0.717) (100 ccs.) and methanol (200 ccs.). Sodium carbonate (3.0 g.) was added and a solution of nitrosomethylurethane in methanol (50 ccs.) slowly run in, over a period of two hours, to the stirred and cooled solution (below 30°). After sixty hours the solution was concentrated to give a brown syrupy mass.

Previous attempts to isolate the product of the ring enlargement, 9- methoxyphenanthrene, by picrate formation and subsequent decomposition, gave only small yields. This syrup was therefore dissolved in benzene and added to a column of alumina (40 x 2"). The column was washed with a mixture of equal parts benzene and petrol ether (60 - 80°) to give the crude methoxy compound (23 g.). This was recrystallised from methanol - colourless glistening needles (20.1 g.) - 54%. M.p. 93 - 95°. Lit. 93 - 94°.

The yield is much larger by this method and the product extremely pure after one recrystallisation.

b) Attempted preparation of 9- methoxy- 10- benzoylphenanthrene.

Attempts to prepare this ketone from the corresponding 9- methoxy- 10- phenanthrenecarboxaldehyde, by oxidation to the 10- acid and subsequent Friedel-Crafts reaction with benzene were abandoned because of the small yields of carboxylic acid obtained from the permanganate oxidation (10%). Another method of synthesis tried was that by a Grignard reaction between the aldehyde above and phenylmagnesium iodide. However only demethylated aldehyde was recovered.

The preparation was then achieved quite simply by a Fries reaction on the benzoyl derivative of 9- hydroxyphenanthrene.

c) 9- Hydroxyphenanthrene.

Reference: L. Fieser, loc. cit.

The methoxy compound a) (15.0 g.) was dissolved in glacial acetic acid (75 ccs.) and hydrobromic acid slowly added. The brown solution was refluxed for two hours to give 10.6 g. - 80% of the demethylated compound - salmon pink needles from benzene m.p. 153 - 155°. Lit., 155°.

d) 9- Hydroxyphenanthrene benzoate.

Reference: Werner, Ann., 321, 302.

The phenol (3.0 g.) when treated with benzoyl chloride in pyridine gave the ester (3.42 g.) - 74% - pale yellow crystals from alcohol m.p. 95 - 96°.

e) 9- Hydroxy- 10- benzoylphenanthrene.

The benzoate (3.30 g.) was dissolved in nitrobenzene (50 ccs.), 10 - 11 g. aluminium bromide added gradually, and the mixture left at room temperature for five hours. After decomposition, and removal of the solvent, a brown oil was obtained which, on extraction with alkali and acidification, gave a dark yellow viscous oil. Trituration in alcohol yielded yellow crystals which were recrystallised from alcohol - lemon yellow needles (0.89 g.) - 27% m.p. 138 - 139°.

This experiment was repeated employing a two hour heating period at 100° but essentially the same results were obtained (30% ketone).

Analysis: Found C - 83.8 ; H - 4.9
Required C - 84.5 ; H - 4.7
(for $C_{21}H_{14}O_2$)

Fission Treatment:-

The ketone (0.37 g.) was refluxed for two hours and, after removal of some acetic acid by distillation, the remainder was poured into water to give a pink solid which was filtered off, washed and dried. This compound recrystallised from benzene as pink needles m.p. 152 - 154°. M.m.p. with 9- hydroxyphenanthrene gave no depression.

Yield - 0.20 g. - 75%.

This treatment was repeated with 0.47 g. ketone and the reaction mixture allowed to stand at room temperature for forty-eight hours. Lemon yellow crystals settled out, and they were filtered off through a sinter glass filter and dried. M.p. 137 - 139° - 0.30 g. starting material.

Water was added to the filtrate and the solution extracted into ether. This ether was shaken up with carbonate and the carbonate extract acidified. No solid was obtained but ether extraction of the acidified solution gave a brownish residue which yielded a few colourless needles from water m.p. 118 - 121°. M.m.p. with benzoic acid 119 - 121°. The hydroxide extract of the original ether solution yielded a brown solid (0.05 g.) which recrystallised from alcohol as yellow needles m.p. 115 - 122°. M.m.p. with starting material 110 - 118°. The depression indicates the presence of some impurity such as 9- hydroxyphenanthrene which must be formed when benzoic acid has been formed.

---

2. 9- Hydroxy- 10- acetylphanthrene.

a) 9- Hydroxyphenanthrene acetate.

This was obtained by refluxing 9- hydroxyphenanthrene with acetic anhydride - colourless needles from petrol ether (60 - 80°). M.p. 77 - 78°.

b) 9- Hydroxy- 10- acetylphenanthrene.

Reference: Mosettig and Burger, J.A.C.S., 1933, 55, 2981.

This ketone was prepared in the same way as the benzoyl analogue above by treatment of the acetate (2.4 g.) with aluminium bromide in nitrobenzene. The solution was kept at room temperature for two and a half hours. The yellow oil obtained was triturated in methanol to give yellow needles (1.15 g.) - 48% m.p. 96 - 97°. Lit. 97°.

Fission Treatment:-

The reddish coloured solution containing the methyl ketone (0.50 g.) dissolved in glacial acetic (15 ccs.) and hydrobromic acid (15 ccs.) was refluxed for two hours and some acetic acid removed (10 ccs.). When the solution was allowed to cool pinkish coloured crystals settled out. These were separated, washed and dried (0.35 g.). They were recrystallised from benzene (0.30 g.) m.p. 154 - 155°. M.m.p. with 9- hydroxyphenanthrene gave no depression.

Yield - 75%.

This treatment was repeated with 0.50 g. ketone, the solution being allowed to stand at room temperature for twenty-four hours. Water was added (50 ccs.) and the brown crystalline solid which formed was filtered off (0.39 g.) m.p. 150 - 152°. M.m.p. - no depression. Recrystallisation raised the m.p. to 155°.

Yield - 0.35 g. - 88%.

---

3. 9- Benzoylphenanthrene.

p. 81

Reference: Bachmann, J.A.C.S., 1934, 56, 1365.

After unsuccessful attempts to prepare this ketone from the Grignard reaction between 9- phenanthrylmagnesium bromide and cyanobenzene in ether-benzene as solvent it was eventually synthesised using benzene only. A colourless complex was obtained when ether and benzene were employed together. This complex was more soluble in benzene however and so the complex was kept in solution with this solvent. With ether-benzene a yellow solid was obtained

which would not form the required ketimide hydrochloride.

Grignard Reaction in benzene:-

9- Bromophenanthrene (10.0 g.) was dissolved in dry benzene (40 ccs.) and magnesium (1.05 g.) added. The reaction was initiated by the addition of an iodine flake and gentle heating. The Grignard solution was refluxed for twelve hours and then cyanobenzene (4.0 g.) was slowly added in a solution of dry benzene (20 ccs.). After heating for an hour the colourless complex settled out but it was dissolved by adding more benzene (150 ccs.). The reaction mixture was worked up by hydrolysing with dilute acetic acid and then shaking the benzene layer with concentrated hydrochloric acid to give a greenish ketimide hydrochloride. This was filtered off and boiled up with water for an hour to produce an almost colourless oil which was extracted with ether and dried. The oil was chromatographed in benzene-petrol ether (1:1) to give a colourless oil.

This oil gradually solidified on standing to give colourless elongated prisms. Recrystallisation was carried out using petrol-ether (40 - 60°) m.p. 79 - 80°. Lit. m.p. 89°. The solid failed to give a dinitrophenylhydrazone derivative.

Analysis:	Found	C - 89.0 ; H - 5.0
	Required (for $C_{21}H_{14}O$)	C - 89.0 ; H - 5.0

An attempt to prepare this ketone from the Grignard between 9- cyanophenanthrene and bromobenzene failed.

Another method tried was the synthesis of the

corresponding alcohol from 9- bromophenanthrene and benzaldehyde. The alcohol could not be oxidised to the ketone however. Potassium dichromate and chromic oxide gave 9:10- phenanthraquinone. Aluminium isopropoxide and acetone, and manganese dioxide in light petroleum gave a recovery of the carbinol only. The ketone failed to give any fission products.

---

4. 9- Benzoyl ~~phenanthrene~~ anthracene.

Reference: Cook, J.C.S., 1926, 1284.

The ketone (1.0 g.) (obtained from anthracene by treatment with benzoic anhydride and aluminium chloride) was refluxed for seven hours. However, after two hours one half of the reaction mixture was removed. A yellow solid was precipitated when the acetic acid was being removed. The ether extract of the diluted solution was extracted with carbonate but no acidic material was found. The original ether extract yielded a yellow solid (0.34 g.) m.p. 140 - 144°. M.m.p. with starting ketone - no depression.

The remaining half of the reaction mixture was investigated after seven hours. Again no trace of benzoic acid could be found. The ether extract gave 9-benzoylanthracene back (0.42 g.) m.p. and m.m.p.

Total recovery - 0.76 g. (76%).

The reaction was repeated with 0.60 g. ketone in a twenty-four hour reflux period. Benzoic acid (0.20 g.) - 77% - was recovered. The ether extract gave a brownish-yellow solid (0.40 g.) which melted over the range 180 - 200°.

This solid was chromatographed on a column (30 x 1.5 cms.). The solid was added in benzene and elution carried out with benzene-petrol ether (60 - 80°). The column separated into a pale yellow, slow moving band, which gave no fluorescence in ultra-violet light, and a faster moving band, colourless in ordinary light but giving a strong blue fluorescence in ultra-violet.

Two main fractions were obtained:

i) Benzene-petrol ether (1:4) - very pale yellow eluate which yielded an almost colourless solid (0.28 g.) m.p. 208 - 211°. M.m.p. with anthracene 207 - 210°.

Bright red trinitrobenzene complex m.p. 162 - 163°. Lit. 163°.

Yield - 72% anthracene.

ii) Benzene-petrol (1:1) - yellow eluate obtained which yielded a pale yellow solid (0.07 g.) m.p. 140 - 142°. M.m.p. with starting material - no depression.

Recovery of ketone - 12%.

---

5. <u>1- Oxo- 4- carboxy- 1:2:3:4- tetrahydrophenanthrene.</u>

1.0 g. of this cyclic ketone was treated with excess of the reagent mixture for twenty-four hours. The diluted solution gave a solid which was extracted into ether (3 x 30 ccs.). The acidified carbonate extract gave a colourless solid which was recrystallised from alcohol

as colourless rhombs (0.85 g.) m.p. 196 - 198°. M.m.p. with starting material 197 - 200°.

The original ether extract of the reaction mixture yielded a small amount of impure starting material (0.05 g.) m.p. 194 - 198°.

Recovery - 0.85 g. to 0.90 g. - 85 to 90%.

---

6. 1:3- Dihydroxyxanthone.

Reference: Nishikawa and Robinson, J.C.S., 1922, 839.

a) Salicyl nitrile.

Attempts to dehydrate the oxime of salicylaldehyde with phosphorous pentoxide or thionyl chloride failed. However dehydration was achieved by heating with acetic anhydride for five hours. This gave the acetylated nitrile which was hydrolysed in 86% yield with sodium ethoxide to give salicyl nitrile m.p. 96 - 97°.

b) 2:2':4:6- Tetrahydroxybenzophenone ketimine.

The nitrile (8.8 g.) and anhydrous phlorogluci-nol (by heating the hydrate at 110° for two hours) (10.0 g.) were dissolved in dry ether (150 ccs.) and dry hydrochloric acid gas bubbled through the solution for sixteen hours. The flask was stoppered and left for three weeks before the red oil, which had settled out, became solid. It was filtered off and boiled with water to give a dark red solid (4.5 g.).

c) 1:3- Dihydroxyxanthone.

The dark red solid (3.0 g.) was dissolved in

dilute sodium hydroxide (5%) and kept at boiling point until the evolution of ammonia had ceased. After cooling, acidification gave a gelatinous precipitate which crystallised from aqueous alcohol as orange-yellow feathery needles m.p. 257 - 259°. Lit. 259°. Yield - 1.70 g.

The xanthone gave a yellow solution with concentrated sulphuric acid which exhibited the characteristic blue green fluorescence of this compound.

Diacetyl derivative - m.p. 144 - 145° - colourless needles from dilute alcohol.

Hydrobromic Acid Treatment:-

The xanthone (0.50 g.) was refluxed for seven hours. On removal of some acetic acid a solid began to settle out. This was filtered off - crude m.p. 254 - 257° (0.48 g.). Recrystallisation from alcohol gave pale yellow needles (0.41 g.) m.p. 256 - 258. M.m.p. - no depression.

Recovery - 80% of pure material.

A twenty-four hour reflux period gave a similar result (75 - 80%).

SECTION V

Quantitative Work on 1- Benzoyl- 2- hydroxynaphthalene.

The purpose of this work was to obtain, by spectrophotometric methods, an idea of the order and rate of the reaction, its duration and the effect of acidity on the reaction velocity.

The spectral measurements were obtained by using the Unicam Spectrophotometer, the solutions being contained in fused quartz cells. Preliminary work was carried out to find out whether the concentrations of the products and the starting ketone could be followed as the reaction proceeded, i.e., the decrease in concentration of the ketone and the consequent increase in concentrations of β - naphthol and benzoic acid produced during the fission process. Therefore the spectra of all three compounds had to be determined separately and examined to see what effect they might have on each other in the reaction medium.

This method of quantitative analysis makes use of the Beer-Bouger Absorption Law which states that absorbance or optical density is proportional to concentration and that absorbances of the components of a mixture are additive. The analyses of two component mixtures are fairly simple but the calculation becomes more complicated for a three component mixture. First of all the spectrum of each compound present has to be determined and compared with the

others to decide which wavelength value will give a strong absorption and at the same time have little or no interference from the absorbances of the other two components. When this has been decided the optical densities at each of these wavelengths have to be measured for each component in the mixture, i.e., three absorbance values are measured using a standard solution of each component giving nine values in all. These values are divided by the appropriate concentrations to give the nine "calibration coefficients" for the three simultaneous equations used to calculate the concentrations of each component in an "unknown" mixture. The equations used for the three component mixtures are as follows (cell width 1.00 cms.):-

$$\underline{\text{At } \lambda x}: \quad A_x = \frac{A^c_{xx}}{C^c_x} \cdot C_x + \frac{A^c_{xy}}{C^c_y} \cdot C_y + \frac{A^c_{xz}}{C^c_z} \cdot C_z$$

$$\underline{\text{At } \lambda y}: \quad A_y = \frac{A^c_{yx}}{C^c_x} \cdot C_x + \frac{A^c_{yy}}{C^c_y} \cdot C_y + \frac{A^c_{yz}}{C^c_z} \cdot C_z$$

$$\underline{\text{At } \lambda z}: \quad A_z = \frac{A^c_{zx}}{C^c_x} \cdot C_x + \frac{A^c_{zy}}{C^c_y} \cdot C_y + \frac{A^c_{zz}}{C^c_z} \cdot C_z$$

The A^c values are calibration absorbances obtained on the three pure substances at concentrations C^c. The A values are absorbances obtained on the unknown mixture at the three wavelengths and the C values are the concentrations to be calculated.

$\lambda_x, \lambda_y, \lambda_z$ are the three suitable wavelengths chosen

from the "pure" or individual spectra. A_{xx}, A_{yy}, A_{zz} are the absorbance values for the three compounds at the positions of least interference. A_{xy} is the absorbance of component Y at the wavelength chosen for component X ("y" indicates that this is a correction due to the interference of Y). Similarly for A_{yx}, A_{xz} etc.

The values of C which are obtained are in gms./litre.

The spectra ($\log \varepsilon$ plotted against λ) of 1- benzoyl- 2- methoxynaphthalene and 1- benzoyl- 2- hydroxynaphthalene are shown in Fig. I. They are, as expected very similar in form and both are rather unremarkable and flat. However, when the spectrum of the second substance is plotted using "absorbance" against wavelength the curve has the form shown in Fig. II with distinct maxima and minima instead of the broad bands of Fig. I in which the maxima are obscure. This appearance of sharp, distinct bands is a useful feature for this quantitative work. The compound used in this work was 1- benzoyl- 2- hydroxynaphthalene because the corresponding methoxy compound would add further complications as a result of the primary demethylation reaction. The spectra of β - naphthol and benzoic acid are also given in Fig. II.

The following maxima were observed:

Wavelengths in millimicrons

Ketone	β- naphthol	Benzoic Acid
250	264	248
330	274	275
365	329	

Comparing the three separate spectra given in Fig. II it is evident that the wavelength where the absorbance due to the ketone should be measured is at the maximum value 365 millimicrons. At this value the interference due to benzoic acid is zero and that due to β- naphthol is practically zero. So the absorbance value measured will be due almost completely to the ketone. It follows that the concentration and changes in concentration of the ketone ought to be measured with a high degree of accuracy. That this is so will be shown later.

Although the absorbance due to β - naphthol is much greater at 274mμ, there is interference from both the ketone, which is absorbing strongly at this wavelength, and benzoic acid which has a maximum at 275mμ. Results showed that this was not a good value for calculations. The other maximum absorbance value (329mμ) has no interference from benzoic acid but a fairly strong interference from the ketone. This was found to be the better position for measuring concentrations of the phenol. The maxima for benzoic acid are quite distinct but unfortunately they correspond closely with a much more strongly absorbing maximum of the ketone (250) and of the phenol (274). So it would appear that the concentrations of the acid in the three component mixtures will not be determinable to any high degree of accuracy. This in fact was so (see results for two and three component mixtures Tables 2 and 3). The value of 280mμ, was found to be the best wavelength for the measurement of absorbance values. Although there is no

maximum at this value it is the position of least interference from either ketone or phenol. All the spectral work was carried out in A.R glacial acetic acid and 48% hydrobromic acid. The "solvent" cells were filled with the same mixture of solvents, care being taken that the relative concentrations of hydrobromic acid in the "solvent" cell and the cell containing the solute, were the same.

Several determinations were carried out using solvent (containing glacial acetic and hydrobromic acids) which had been refluxed for the same times as the reaction mixture medium. However this was found to be unnecessary because the same optical density readings were obtained using an untreated solvent mixture.

Summary of results on standard mixtures.

Table 2. Two Component Mixtures

	Ketone		β - naphthol		Benzoic Acid	
	Conc. in gms./litre		Conc. in gms./litre		Conc. in gms./litre	
	Found	Actual	Found	Actual	Found	Actual
1.	0.0488	0.0485	0.0361	0.0360		
2.	0.0549	0.0548	0.0433	0.0430		
3.			0.0422	0.0399	0.1134	0.0903
4.			0.0592	0.0581	0.0625	0.0573

Table 3. Three Component Mixtures

	Ketone		β - Naphthol		Benzoic Acid	
	Conc. in gms./litre		Conc. in gms./litre		Conc. in gms./litre	
	Found	Actual	Found	Actual	Found	Actual
1.	0.0250	0.0250	0.0380	0.0439	0.0378	0.0335
2.	0.0555	0.0557	0.1317	0.1288	0.0274	0.0229
3.	0.0542	0.0536	0.0228	0.0216	0.0334	0.0405
4.	0.0570	0.0572	0.0548	0.0648	0.0523	0.0579

These results show that the concentration of ketone in all the mixtures studied can be accurately determined, the error being of the order 0.2 - 0.25%. However, there is a considerable decrease in accuracy in the case of β - naphthol. In the two component mixtures of β - naphthol and ketone the concentrations of both are fairly accurate but with two component mixtures of the phenol and benzoic acid the accuracy in determining the concentration of phenol has fallen and the concentrations of benzoic acid, as measured, do not correspond at all well with the known concentrations of acid added. As mentioned earlier, this is to be expected because of the much more strong ketonic and phenolic absorptions in this region of the spectrum. Attempts were made to increase the accuracy of the values measured for the acid by using absorbance values at wavelengths 248, 270 and 274 millimicrons but the values given (at 280 mμ) were the most accurate. The absorbance values obtained for 248 mμ were of no use primarily because of the strong interference of the ketone and also because the actual optical density readings from the instrument were found to be much less

accurate and difficulty was observed in trying to reproduce them. At wavelengths below 255 mμ, excessive slitwidths and the lowest sensitivity had to be employed to give reasonable readings. This difficulty is due, of course, to the polar nature of the solvent used. Absorption readings could not be obtained below 225 - 230 mμ, whereas in solvents such as ethanol and cyclohexane spectral readings can be continued much lower with reasonable accuracy. This is therefore another point in favour of the choice of 280 mμ as the wavelength for taking values since the accuracy of the measurements is much higher. In addition there is less interference from the other two components although 280 mμ does not represent a maximum in the benzoic acid curve.

To the reasons already mentioned for this reduction in accuracy there may be added the possibility of some chemical interaction between the products of the reaction β - naphthol and benzoic acid to give for example the benzoate. This effect may be quite important because the concentrations of β - naphthol, as measured, only digress from the true, weighed values when benzoic acid is present (cf. the two component mixtures in Table 2). There are other possibilities, such as dimerisation of the acid, and other solvent effects which might help to account for this failure to measure the concentrations of phenol and acid accurately.

The most important effect must be the interference phenomenon however because of the much larger absorption of one component compared to another cf. Fig. III which

gives two typical curves for the three component mixture with maxima at 362, 330 and 254 mμ. They show what happens to the absorbance values when all three components are present. The absorption maxima at 362 and 320 mμ are not affected much. In contrast, the absorbance values obtained at the 254 mμ maximum have increased tremendously due to the large absorbance of the ketone and phenol and the smaller one of benzoic acid.

From these results with two and three component mixtures it is evident that, for accurate work, only the concentration of the ketone is measurable with any high degree of accuracy. The concentration changes of the phenol may be followed roughly but not those of the acid. Therefore only concentration changes of the ketone were followed in attempting to obtain some idea of the rate of the reaction and the effect of acidity on the rate.

Results of Fission Reactions.

A typical reaction will be described. A weight of 0.17165 g. of the ketone was dissolved in 20.00 mls. of A.R redistilled glacial acetic acid and 5.00 mls. freshly distilled 48% hydrobromic acid added. The greenish yellow solution was refluxed and samples of 1.00 mls. taken at intervals. This sample was diluted to 10.00 mls. in a standard flask with acetic acid and absorbance values measured at 365, 329 and 280 mμ.

Table 4.

Results:-

Solution I

Time (hrs.)	Wt. of ketone left (g.)	Calculated wt. of phenol (g.)	Actual wt. β - naphthol (g.)	% Ketone left	% Ketone used up
1	0.09900	0.04215	0.04203	57.7	42.3
1½	0.07155	0.05812	0.05564	41.7	58.3
3	0.03674	0.07832	0.07201	21.4	78.6
4	0.02854	0.08328	0.07371	16.6	83.4
5	0.01446	0.09128	0.07884	8.4	91.6
6	0.00943	0.09417	0.07965	0.6	99.4

In this set of results (Table 4) with a reaction time of six hours it was found that 42.3% of the ketone had been reacted upon after one hour and the reaction was almost complete after six hours. It will be noted that in this case the actual weights of ketone were calculated at the various times in order to show the effect of the difference between calculated and actual weights of β- naphthol is that obtained from the weight of ketone which has decomposed and the actual weight is that obtained from the C_y value of the equation (p. 154). (The weight of ketone is obtained from the corresponding C_x value.) It must be noted that there is reasonable concordancy between the two values for the phenol at the smaller concentration values but the divergence becomes quite large at the larger concentrations, i.e., when the reaction has proceeded for four or five hours. This falling off in accuracy is to be expected in view of the earlier discussion. The reaction medium at the start contains mostly ketone with a little phenol and acid but as the reaction proceeds all the interference phenomena become apparent.

In the subsequent results the values are given in concentrations of ketone in gms./litre, i.e., the actual C_x value calculated from the equation. The above results show that the concentration of phenol cannot be followed accurately and so the results given involve the ketone only. Since the fission was nearly 45% complete in an hour it was decided to take samples at fifteen minute intervals over the first hour.

Table 5.

	Solution I		Solution II		Solution III		
Time (hrs.)	C_x	log C_x	C_x	log C_x	C_x	log C_x	Average % ketone used up
0	6.866	0.8367	7.412	0.8699	2.421	0.3840	0
0.25			5.929	0.7730	1.878	0.2737	18
0.50			5.150	0.7118	1.520	0.1818	35
0.75			4.697	0.6719	1.270	0.1038	42
1	3.965	0.5982	4.132	0.6163	1.071	0.0253	48
2	(1.5) hrs. 3.111	0.4929	2.367	0.3742	0.5659	$\bar{1}$.7527	67
3	1.670	0.2227	1.410	0.1492	0.3097	$\bar{1}$.4910	82
4	1.359	0.1332	0.9959	$\bar{1}$.9982	0.1760	$\bar{1}$.2455	88
5	0.7230	$\bar{1}$.8591	0.7114	$\bar{1}$.8521	0.1074	$\bar{1}$.0266	93
6	6.4963	$\bar{1}$.6958	0.5009	$\bar{1}$.6998	0.0673	$\bar{2}$.8280	97

The concentrations of ketone were plotted against time for each of the three solutions shown above (cf. Fig. IV). In each case reasonably good exponential type curves were obtained. The graph of logarithm of ketone concentration against time was then drawn for each solution (Fig. V), and good straight line correlation was found if the concentration values over the first hour were disregarded. The values (for solutions II and III) did not fit into the straight line relationship. This may be because of the method of sampling which involves a time lag of a few minutes during the taking of a sample (for drainage of the condenser etc.). This lag is relatively large over the shorter reaction times of the first hour but becomes less so later on.

This straight line relationship indicated that the reaction followed first order kinetics with respect to the ketone. The rate constants "k" were therefore calculated using the formula:-

$$k = \frac{2.303}{t_2 - t_1} \cdot \log_{10} \frac{(a - x_1)}{(a - x_2)}$$

where $(a - x_1)$ and $(a - x_2)$ are the concentrations at time t_1 and t_2; 'a' is the initial concentration x_1 and x_2 the fall in concentration in times t_1 and t_2 respectively.

Table 6.

	Solution I		Solution II		Solution III	
Time (hrs.)	Conc. g/l.	k (sec^{-1})	Conc. g/l	k (sec^{-1})	Conc. g/l	k (sec^{-1})
0	6.866		7.412		2.421	
1	3.965	0.00015	4.132	0.00014	1.071	0.00023
2 (1.5) →	3.111	0.00014	2.367	0.00016	0.5659	0.00017
3	1.670	0.00012	1.410	0.00014	0.3097	0.00017
4	1.359	0.00006*	0.9959	0.00010	0.1760	0.00016
5	0.7230	0.00018	0.7114	0.00009	0.1074	0.00014
6	0.4963	0.00010	0.5009	0.00010	0.0673	0.00015
Average "k":		0.00014		0.00012		0.00017

* In averaging, this value was left out as it is obviously in error.

The rate constant values for the concentrations measured over the first hour were not calculated as the graph of "logarithm concentration against time" (Fig. V) showed that they did not fit into this relationship. This is probably due to the method of sampling, as mentioned above, of the reaction solutions over the first hour. The time for sampling is not so important in the later stages.

The values of "k" calculated for each sample show reasonable concordancy and the average values for each set of values agree quite well and so it would appear that the reaction is first order with respect to the ketone.

The next problem to be investigated was the effect of acidity on the rate of the reaction. It was decided to carry out the reaction in a solution of dichloracetic and hydrobromic acids to see if the increased acidity due to the replacement of acetic with dichloracetic would increase the rate of ketonic fission.

As before 20 mls. dichloracetic were used with 5 mls. of hydrobromic acid and samples taken at intervals. The reaction flask was heated in an oil bath at the same temperature as the glacial acetic mixture. However it was noted that a deeply coloured solution was obtained on refluxing. This colour had an effect on the spectral results and they were found to be quite abnormal and haphazard (Table 7).

Table 7.

Time (hrs.)	% Ketone used up
0	0
0.25	82
0.50	81
0.75	81
1.0	82
2	81
3	84
4	74
5	76
6*	67

This table gives the percentage of ketone used up during the reaction. Up to a reaction time of three hours the percentage is reasonably steady at 80 - 82% but thereafter a decrease takes place. Why this should be so is not known but presumably the deep red solution which is formed is due to the formation of some compound during the reaction. The fact that the percentage of ketone used up between zero time and three hours is of the order of 80% which is higher than the percentage used up in the case of acetic acid (see Table 5), would appear to suggest that the acidity of the solution is having the expected effect of speeding up the reaction. This increase in percentage using dichloracetic was also shown in the large scale reactions (p. 141).

To show definitely what effect a change in acidity

would have it was decided to change the concentrations of hydrobromic acid present by adding water in varying amounts. The reaction velocities could then be calculated and compared with the values obtained above (Table 6).

Table 8.

	Solution IV			Solution V			Solution VI		
Time (hrs.)	Conc. (Cx) g/l.	log Cx	k (sec^{-1})	Conc. (Cx) g/l.	log Cx	k (sec^{-1})	Conc. (Cx) g/l.	log Cx	k (sec^{-1})
0	4.934	0.6932		4.859	0.6865		6.147	0.7887	
1	1.549	0.1900	0.00013	3.850	0.5855	0.000063	5.620	0.7497	0.000025
2	0.9847	$\bar{1}$.9933	0.00013	3.332	0.5227	0.000040	5.347	0.7281	0.000014
3	0.7805	$\bar{1}$.8924	0.00007	2.849	0.4547	0.000044	5.097	0.7073	0.000013
4	0.4870	$\bar{1}$.6875	0.00013	2.418	0.3834	0.000046	4.905	0.6906	0.000011
5	0.3492	$\bar{1}$.5431	0.00010	2.021	0.3056	0.000049	4.730	0.6749	0.000010
6	Readings too small			1.693	0.2287	0.000049	4.459	0.6493	0.000016
8				1.151	0.0611	0.000054	3.967	0.5985	0.000016
	Average "k":		0.00011			0.000047			0.000013

Solution IV (Table 8) contained 20 mls, acetic acid and 10 mls. hydrobromic acid which is double the normal amount of the latter. The rate constant remained almost the same however presumably because the concentration of hydrobromic acid is in great excess with 5 mls. of the acid present and so the addition of 10 mls. will have no effect on the reaction rate. The constant "k" is again in good agreement with those obtained for the earlier mixtures investigated (Table 6) and the logarithm plot gave good straight line concordancy with a slope similar to those of the earlier solutions (Fig. V). The average "k" value for the four solutions investigated is 0.00014 (sec^{-1}).

When water was added to the reaction mixture, as in Solutions V and VI (Table 8), changes were found to occur. In Solution V the hydrobromic concentration was changed. This solution contained 20 mls. glacial acetic acid, 5 mls. hydrobromic acid and 2.5 mls. water. Solution VI contained the same quantities of the first two liquids but 5 mls. of water were added. A visible reduction in reaction rate is shown by the decrease in slope of the graphs for Solutions V and VI (Fig. V). The slope for the latter is practically zero. The corresponding "k" values have also dropped to 0.000047 and 0.000013 respectively. This illustrates quite clearly the dependence between the rate of the fission reaction and the acidity of the reaction medium. From this rough proportionality between rate and acidity several conclusions can be made regarding the mechanism of the reaction (p. 89).

BIBLIOGRAPHY

1. Blatt, Chem. Reviews, 1940, 27, 413.
2. Baker, J.C.S., 1952, 1825.
3. Baker, McOmie and Ullricht, J.C.S., 1937, 478.
4. Joshi and Shah, J. Ind. Chem. Soc., 1954, 31, 325.
5. Leonard & Hyson, J. Org. Chem., 1948, 13, 164.
6. V. Auwers and Mauss, Ann., 1928, 460, 40.
7. Baddeley, J.C.S., 1943, 273.
8. Mosettig & Burger, J.A.C.S., 1933, 55, 2981.
9. Bruce, Sorrie and Thomson, J.C.S., 1953, 2403.
10. Sekera, Trans Illinois State Acad. Science, 1935, 27, 81. (C. Abs., 29, 3671).
11. Rosenmund and Schnurr, Ann., 1928, 460, 56.
12. Woodham, Thesis Edin., 1951, p. 88.
13. Fieser, J.A.C.S., 1931, 53, 3558.
14. Louise, Ann. Chim., 1885, 6, 206.
15. Klages and Lickroth, Ber., 1899, 32, 1549.
16. V. Auwers et al., Ann., 1926, 447, 176.
17. V. Auwers and Mauss, Ber., 1928, 61, 1502.
18. Muhr, Ber., 1895, 28, 3215.
19. Weiler, Ber., 1899, 32, 1908.
20. Elbs, J. Prakt. Chem., 1887, 35, 465.
21. Cook, J.C.S., 1926, 1282.
22. Royer, Bull. Soc. Chim., 1953, 412.
23. Royer and Bisagni, Bull. Soc. Chim., 1954, 486.
24. Chalvet, Royer et al., Bull. Soc. Chim., 1954, 807.

25. Scholtz, Ber., 1912, 45, 734.

26. Borrows, Holland & Kenyon, J.C.S., 1946, 1069.

27. Wilson, J.C.S., 1945, 63.

28. Ochiai et al., J. Pharm. Soc. Japan, 1938, 58, 627.

29. Borrows and Holland, Chem. Revs., 1948, 42, 636.

30. Claus, Ber., 1886, 19, 2880.

31. Hoogewerff and Van Dorp, Rec. Trav. Chim. Pays Bas, 1902, 21, 349.

32. Fischer and Giebe, Ber., 1898, 31, 545.

33. Morgan and Coulson, J.C.S., 1929, 2209.

34. Meyer, Ber., 1895, 28, 1269.

35. Klages and Stamm, Ber., 1904, 37, 1717.

36. Stoermer, Ber., 1908, 41, 321.

37. Koenigs, J. Prakt. Chem., 1900, 61, 26.

38. Hill and Short, J.C.S., 1935, 1123.

39. Buu-Hoi and Cagnaint, Rec. Trav. Chim. Pays Bas, 1948, 67, 53.

40. Buu-Hoi and Cagnaint, Compt. rend. 216, 299.

41. Anderson and Thomas, J.A.C.S., 1943, 65, 238.

42. Hill, Short and Stromberg, J.C.S., 1937, 1619.

43. Butenandt and Schramm, Ber., 1935, 68, 2083.

44. Haberland, Ber., 1936, 69, 1380.

45. Muhlemann, Pharma. Act. Helv., 24, 356.

46. Decombe, Bull. Soc. Chim., 1945, 651.

47. Johnson and Heinz, J.A.C.S., 1949, 71, 2913.

48. Bradsher and Vingiello, J. Org. Chem., 1948, 13, 786.

49. Berliner, J.A.C.S., 1944, 66, 533.

50. Bradsher and Vingiello, J.A.C.S., 1949, 71, 1434.

51. Galloway, Reid and Stafford, Chem. and Ind., 1954, 724.

52. Haller and Bauer, Compt. rend., 1908, 147, 824.

53. Schonberg, Ann., 1924, 436, 205.

54. Lea and Robinson, J.C.S., 1926, 2351.

55. Schonberg and Mustafa, J.C.S., 1946, 642.

56. Cazeneuve, Bull. Soc. Chim., 1896, 15, 72.

57. Brown, Hammick & Scholefield, J.C.S., 1950, 778.

58. Fieser and Fieser, Organic Chemistry (Sec. ed.), 702.

59. Baker, J.C.S., 1934, 1953.

60. Johnson and Melhuish, J.C.S., 1947, 346.

61. Springall et al., J.C.S., 1949, 1524.

62. Berthier and Pullmann, Bull. Soc. Chim., 1950, 17, 88.

63. Baker, J.C.S., 1952, 1825.

64. Bachmann, J.A.C.S., 1934, 56, 1365.

65. Schenkel and Schenkel-Rudin, Helv. Chim. Acta, 1948, 31, 514.

66. Schubert, J.A.C.S., 1949, 71, 2639.

67. Graebe and Ullmann, Ber., 1896, 29, 824.

68. Johnson and Glenn, J.A.C.S., 1949, 71, 1092.

69. Hoesch, Ber., 1915, 48, 1130.

70. Votocek and Potmesil, Chem. and Ind. 1916, 35, 731.
Ber., 1916, 49, 1185.

71. Gomberg and Cone, Ann., 1910, 376, 237.

72. Powell, J.C.S., 1948, 71.

73. Organic Syn., 21, 23.

74. Hamada, Science Reports Tohoku Imp. Univ. First Ser., 1933, 22, 55.

75. Chakravarti and Bera, J. Ind. Chem. Soc., 1944, 21, 109.

76. Orndorff and Lacey, J.A.C.S., 1927, 49, 818.

77. Meisenheimer et al., J. Prakt. Chem., 1928, 119, 338.

78. V. Auwers and Janssen, Ann., 1930, 483, 44.

79. Montagne, Rec. Trav. Chim. Pays Bas, 1908, 27, 355.

80. Elbs, J. Prakt. Chem., 1887, 35, 488.

81. Kruber and Schmieden, Ber., 1939, 72B, 653.

82. Braun and Witt, Ber., 1914, 47, 3216.

83. Fries, Ber., 1921, 54, 711.

84. Fierz-David and Jaccard, Helv. Chim. Acta, 1928, 11, 1042.

85. I. G. Farbenind, C.A. 1929, 2187.

86. Jambuserwala, Holt and Mason, J.C.S., 1931, 374.

87. Hill and Melhuish, J.C.S., 1935, 1161.

88. Adams and Levine, J.A.C.S., 1923, 45, 2377.

89. Bogert and Howells, J.A.C.S., 1930, 52, 840.

90. Ullmann and Sponagel, Ann., 1906, 350, 92.

91. Fieser, Jacobsen and Price, J.A.C.S., 1936, 58, 2163.

92. Schultz et al., J.A.C.S., 1940, 62, 2902.

93. Werner, Ann., 321, 302.

94. Nishikawa and Robinson, J.C.S., 1928, 839.

ACKNOWLEDGEMENTS

The author wishes to express his sincere gratitude to Dr Neil Campbell for his constant enthusiasm and advice during this work.

Thanks are also due to the Anglo-Iranian Oil Company for a grant.

FIG. I.

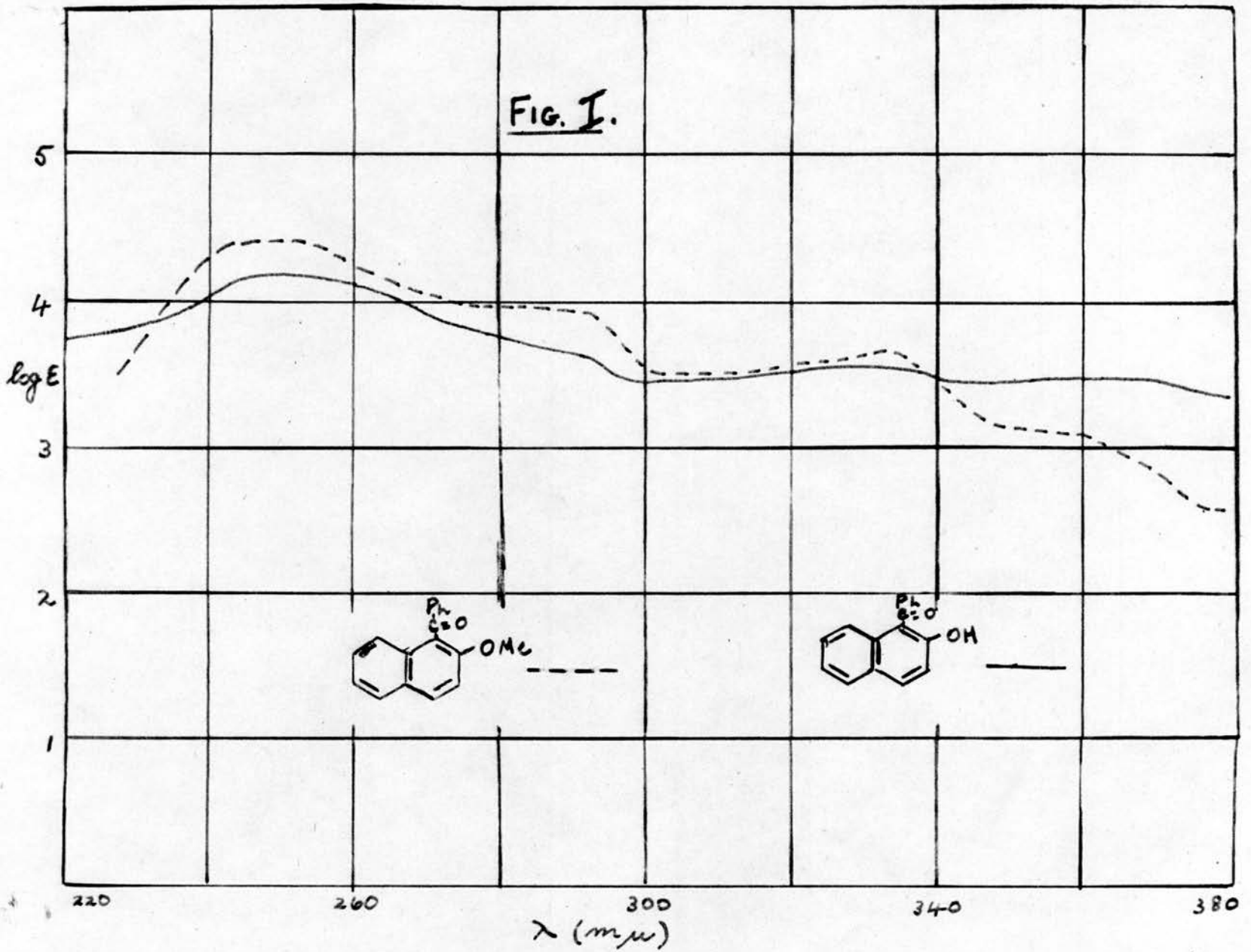


FIG. II.

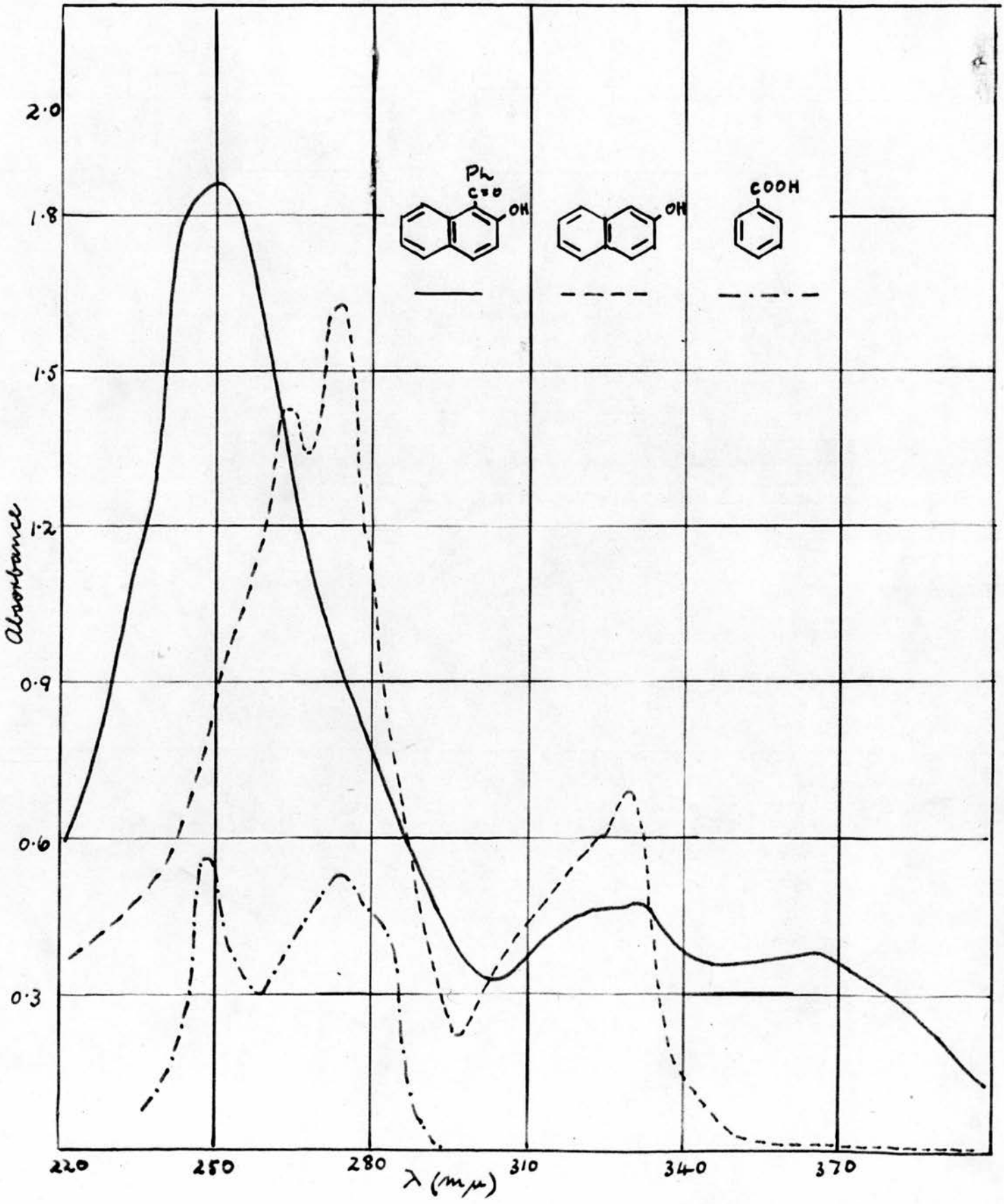
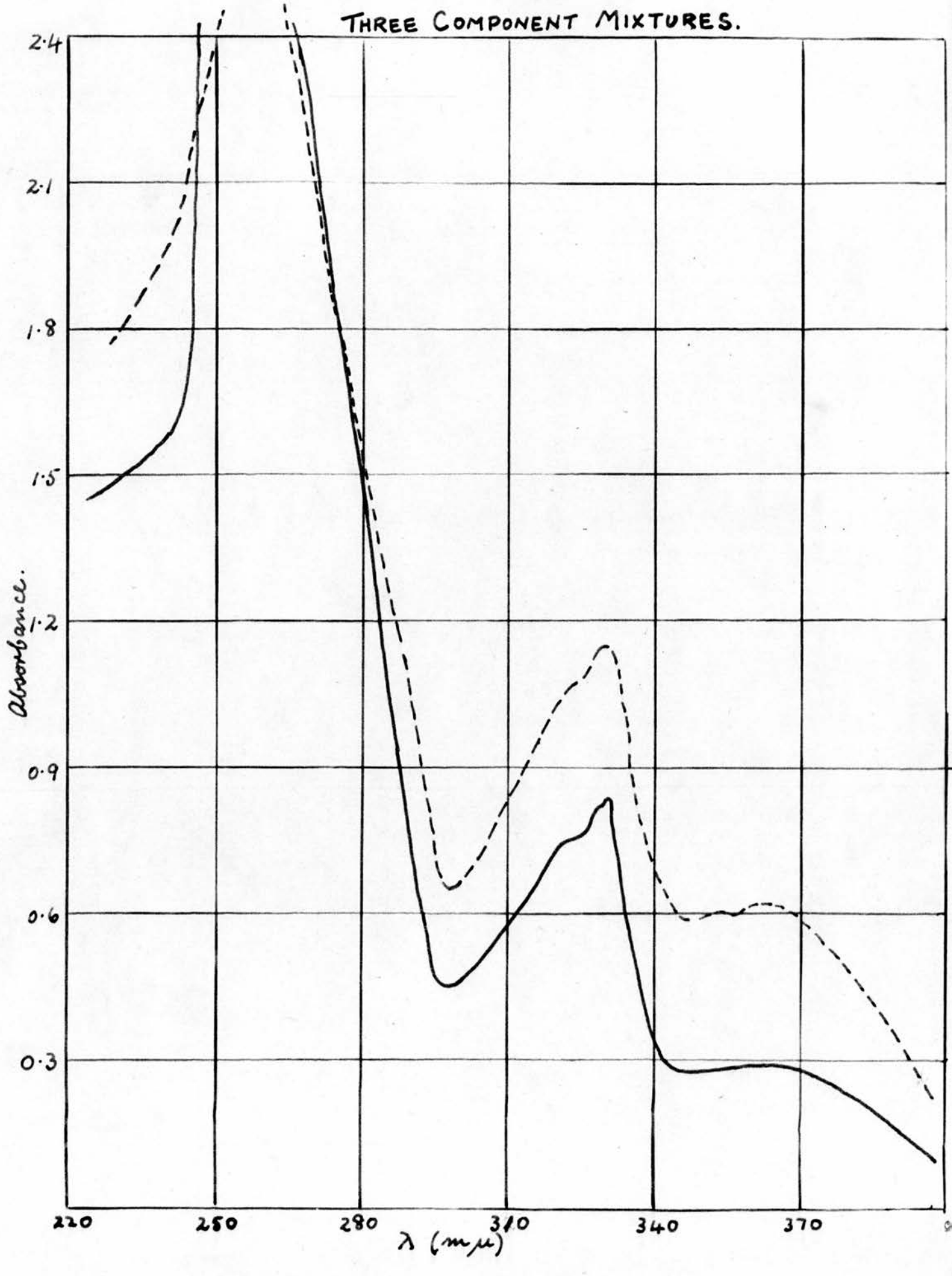

Ph
C=O
OH
OH
COOH
2·0
1·8
1·5
1·2
0·9
0·6
0·3
Absorbance
220
250
280
310
340
370
λ (mμ)

FIG. III.

THREE COMPONENT MIXTURES.



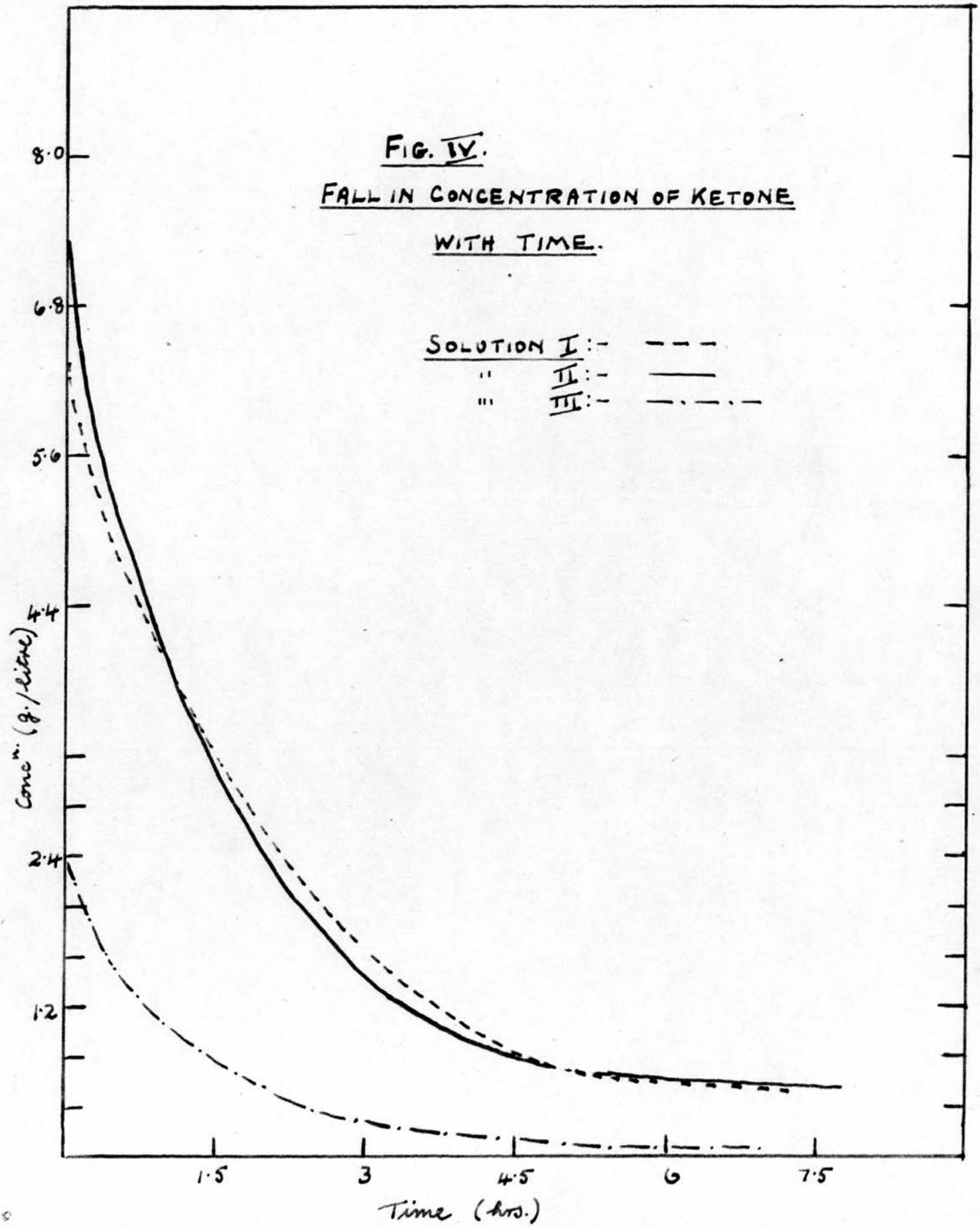


FIG. IV.
FALL IN CONCENTRATION OF KETONE WITH TIME.
SOLUTION I :-
" II :-
" III :-
8·0
6·8
5·6
4·4
2·4
1·2
Conc^n. (g./litre)
1·5
3
4·5
6
7·5
Time (hrs.)

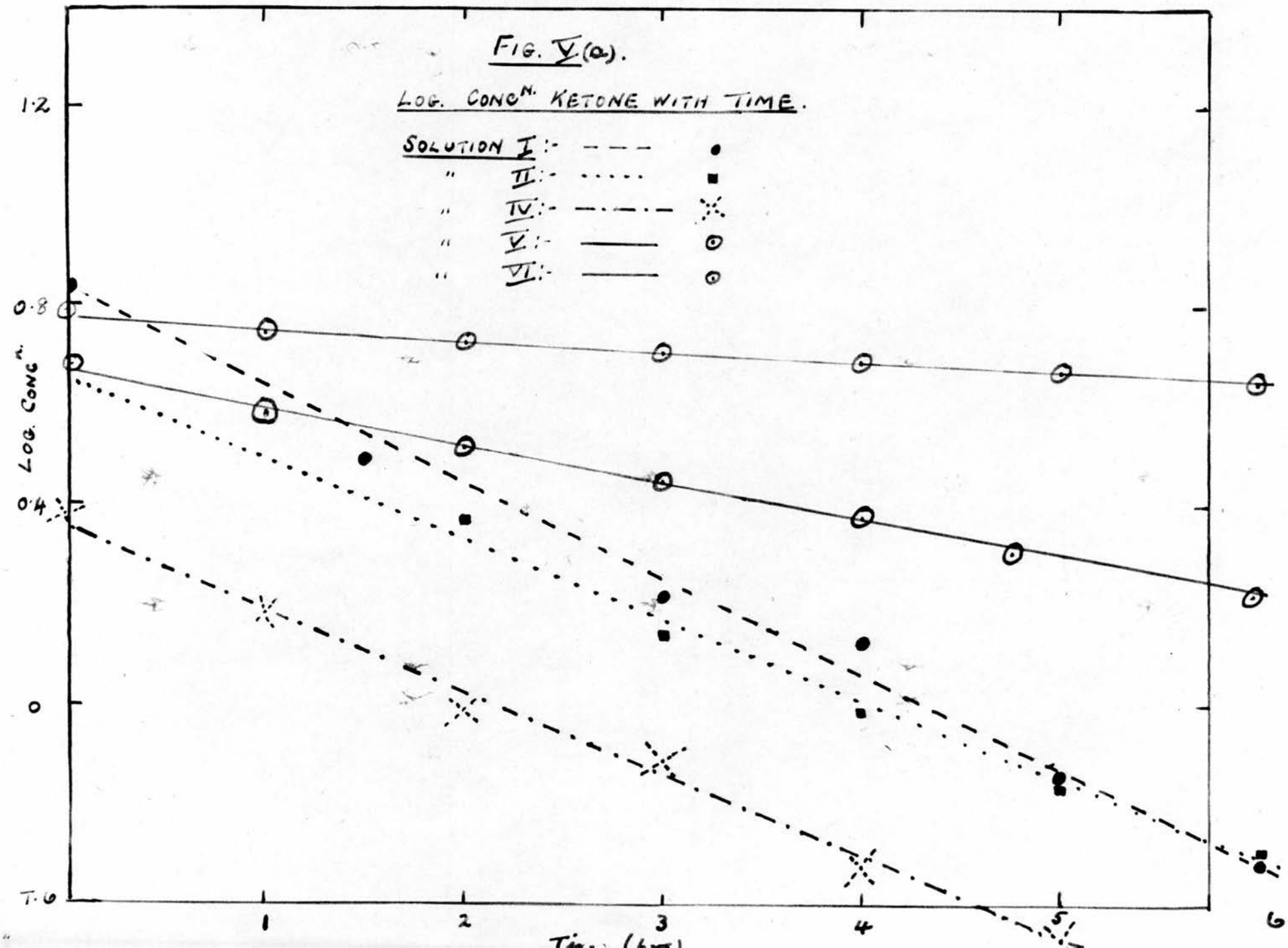


FIG. V (a).
LOG. CONCN. KETONE WITH TIME.
SOLUTION I :-
" II :-
" IV :-
" V :-
" VI :-
1·2
0·8
0·4
0
T·6
LOG. CONCN.
1
2
3
4
5
6

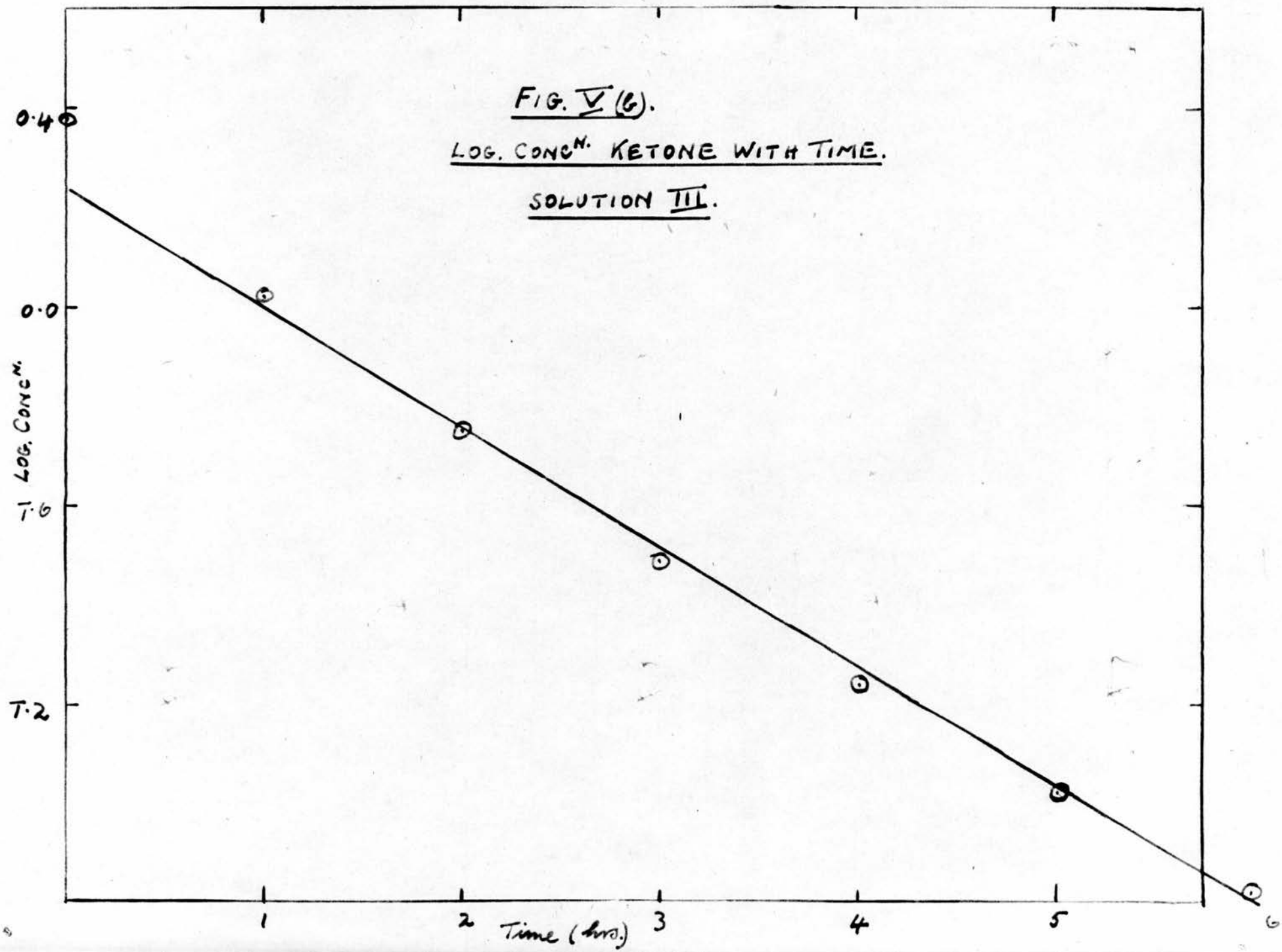


FIG. V (6).
LOG. CONCN. KETONE WITH TIME.
SOLUTION III.
0·4
0·0
T·6
T·2
- LOG. CONCN.
1
2
3
4
5
Time (hrs.)